PHD

Approaches to lipoxygenase inhibitors

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Award date:
1987

Awarding institution:
University of Bath

APPROACHES TO LIPOXYGENASE INHIBITORS

submitted by RAYMOND JOHN BOUCHER

for the degree of

Doctor of Philosophy

of the University of Bath

1987

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For Sue

ACKNOWLEDGEMENTS

I would like to thank my supervisors, Professor M.M. Campbell and Dr. A. Campbell, for all of their good advice and guidance during the time of this research.

Thanks to Dr. D. Brown whose help with nmr spectra was invaluable.

Thanks are also due to the technicians who operate the mass spectrometry and nmr services, Harry Hartell, Dave Wood and Chris Cryer, and to the two Richards who gave me technical assistance during my time at Bath, i.e. Richard Hunter and Richard Betteridge.

I would like to express my thanks to Wilson, Drew, Maurice and everyone who helped me at Organon in Scotland.

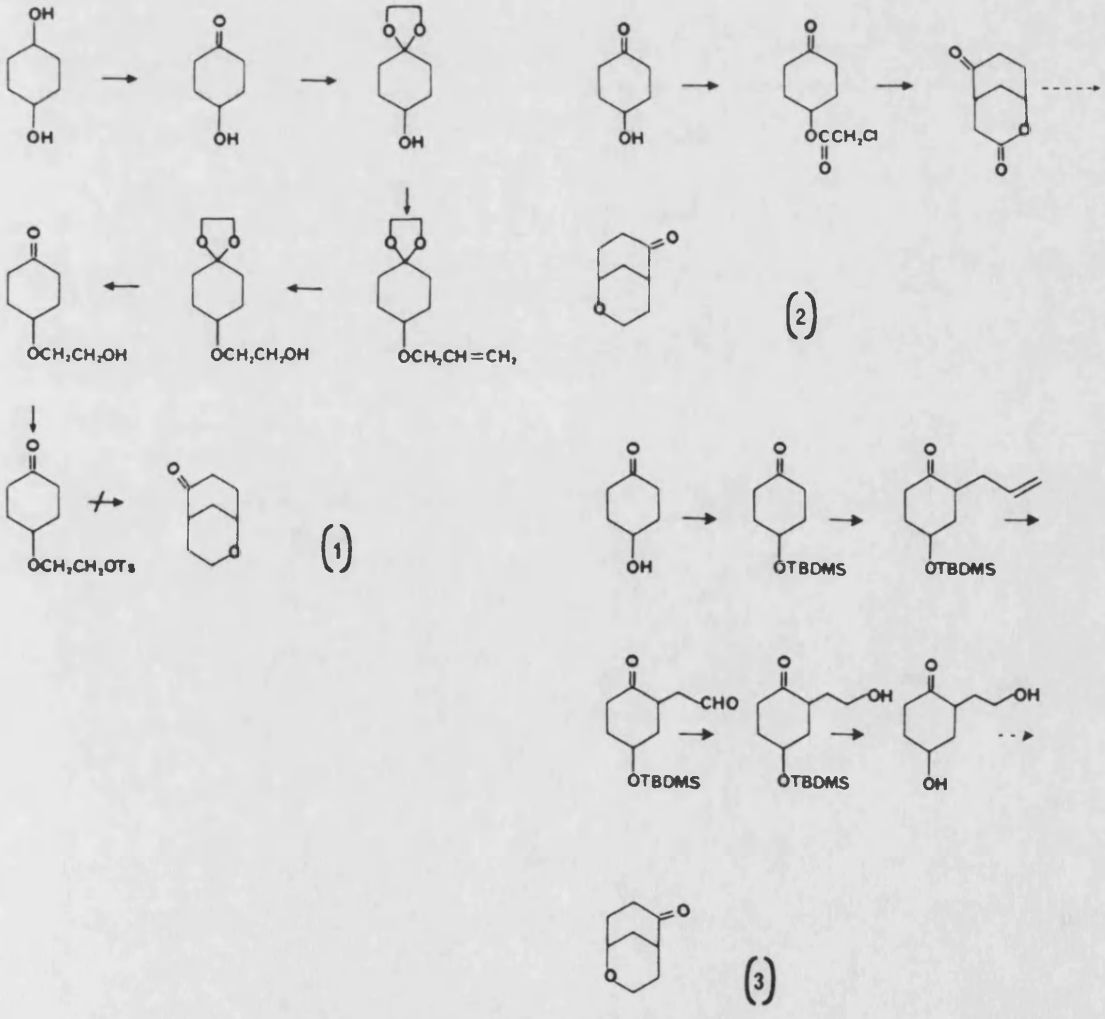
I should like as well to thank Sue, who gave me considerable help, and whose help blossomed into a great deal more.

Many thanks are due to Helen Hobbs, who took on the job of typing this thesis, mastered my writing and has produced a beautiful document.

And, finally, I would like to thank my parents who have supported me throughout my education.

ABSTRACT

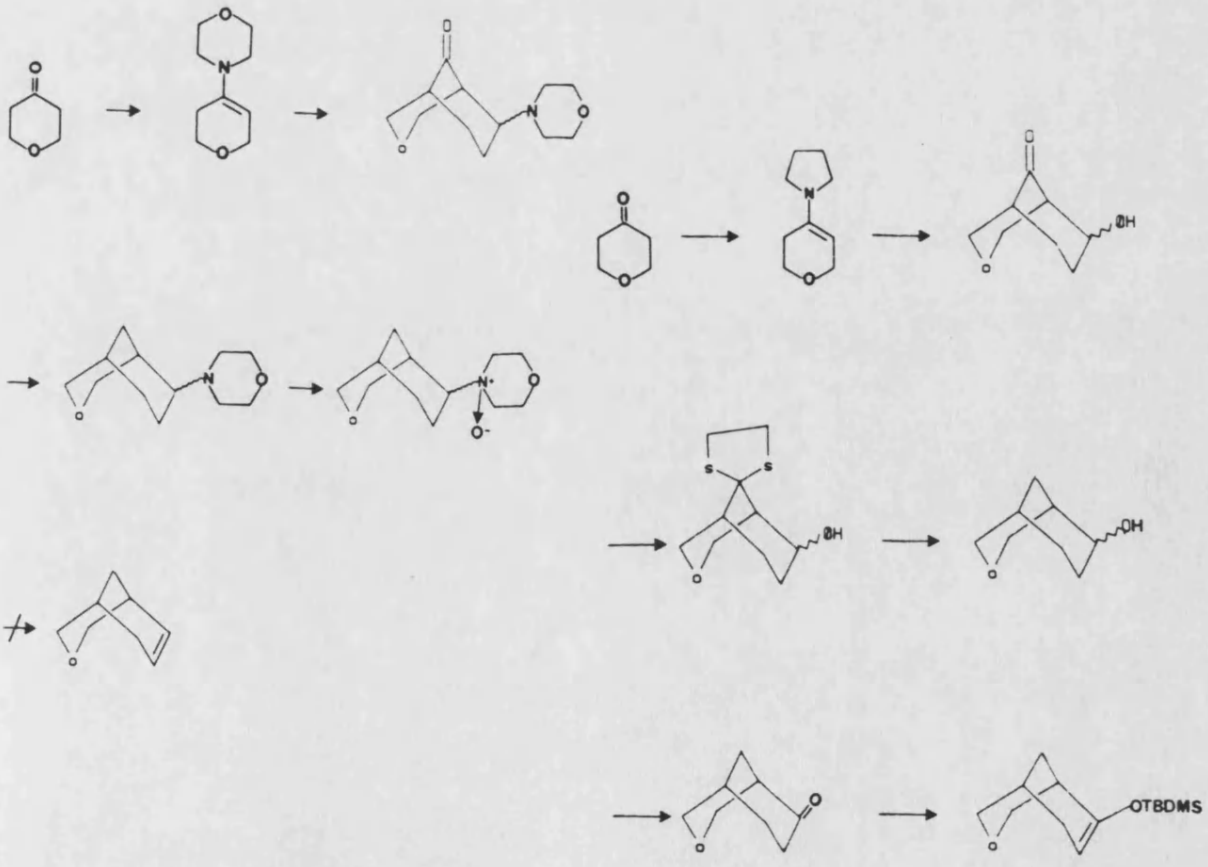
Three approaches to the synthesis of 2-oxabicyclo [3.3.1]nonanes are described. The first route involved the attempted cyclisation of 4-ethoxycyclohexanones via an internal enolate alkylation process. A β-oxygen effect was postulated as the reason for failure of these cyclisations. The second route utilised the same internal enolate alkylation process, but using 4-chloroacetoxy-cyclohexanone, but this failed as the substrate was too reactive under the conditions, giving a mixture of products. The third route involved the attempted cyclisation of disubstituted cyclohexanones.



The synthesis of a range of 3-oxabicyclo[3.3.1]nonanes are described, which were synthesised by the reaction of either the morpholine or pyrrolidine enamine of tetrahydropyran-4-one with acrolein. Under anhydrous conditions the products were 6-morpholino or 6-pyrrolidinyl 3-oxabicyclo[3.3.1]nonan-9-ones but under aqueous conditions, exo and endo 6-hydroxy 3-oxabicyclo[3.3.1]nonan-9-ones were obtained. These structures were assigned on the basis of detailed spectroscopic analysis.

The synthesis of the trimethylsilyl and t-butyldimethyl silyl enol ethers of 3-oxabicyclo[3.3.1]nonan-6-one are described and were obtained in good yield.

The ^{13}Cnmr spectra of various 3-oxabicyclo[3.3.1] nonanes were compared and their conformation were assigned by comparison with data from bicyclo[3.3.1]nonanes.



The trimethylsilyl and t-butyldimethylsilyl enol ethers of 3-oxabicyclo[3.3.1]nonan-6-one were ozonolysed to give the bifunctional products 5-(2-formylmethyl)-3-tetrahydropyran carboxylic acid and 5-(2-formylmethyl)-3-tetrahydropyranmethyl t-butyldimethylsiloxycarbonyl respectively in good yields. 5-(2-Formylmethyl)-3-tetrahydropyran carboxylic acid was found to be a very useful synthetic relay compound.

A number of Wittig reactions were attempted in order to elaborate the side chains. The Wittig reaction of 5-(2-formylmethyl)-3-tetrahydropyran carboxylic acid with n-hexylphosphonium bromide to give 5-(cis-2-octenyl)-3-tetrahydropyran carboxylic acid is described.

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ACRONYMS

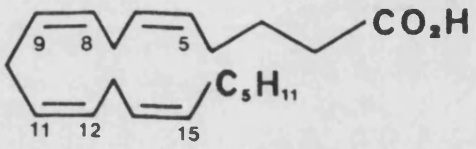
AA	Arachidonic acid
Bu_4NF	tetra-n-Butylammonium fluoride
^tBuOK	Potassium-t-butoxide
DBU	1,8-Diazabicyclo[5.4.0.]undec-7-ene
DCM	Dichloromethane
DMAP	4-Dimethylaminopyridine
DME	Dimethoxyethane
DMF	Dimethylformamide
DMSO	Dimethylsulfoxide
EA	Ethyl acetate
HMPA	Hexamethylphosphoramide
LAH	Lithium aluminium hydride
LDA	Lithium diisopropylamide
MsCl	Methanesulphonylchloride
$NaBH_4$	Sodium borohydride
NaH	Sodium hydride
PE	Petroleum ether 60-80°
PTSA	p-Toluene sulphonic acid
Py	Pyridine
TBDMS	t-Butyldimethyl silyl
THF	Tetrahydrofuran
TMS	Trimethyl silyl

INTRODUCTION

1. Introduction

1.1 Background

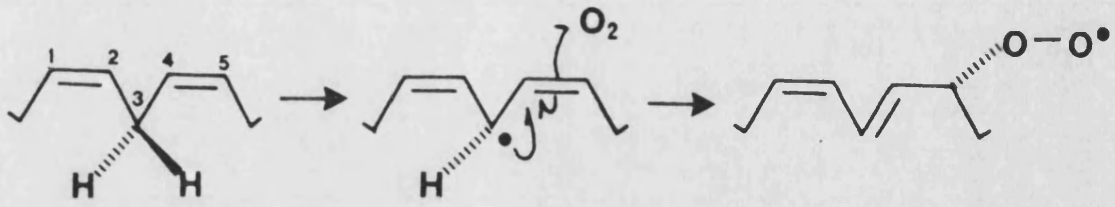
Lipoxygenases are iron containing dioxygenases, that characteristically incorporate two atoms of molecular oxygen into a substrate. The lipoxygenases give rise to a number of primary metabolites from arachidonic acid (1), which all involve a hydroperoxy group; these can occur at positions 5,8,9,11,12,15.



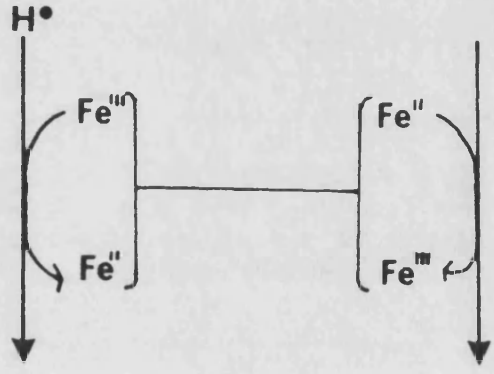
(1)

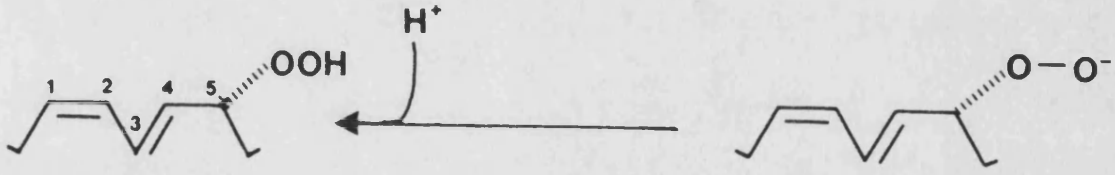
The lipoxygenases family of enzymes catalyse the oxidation of a cis,cis,1,4 pentadiene unit within arachidonic acid to a trans-2,cis-4 dien-5-hydroperoxy moiety[1], which are then converted to a hydroxy compound (hydroxy-eicosatetrenoic acid (HETE'S)) by a reductase enzyme, probably by glutathione in the presence of glutathione peroxidase (see Scheme 1).

Theories on the mechanism of lipoxygenases are based on what is known about the process of fatty acid auto-oxidation which occurs spontaneously in the presence of oxygen, light and metal ions. This process is initiated by abstraction of a hydrogen radical from the methylene group of a cis,cis,1,4 pentadiene moiety. This results



PENT-1,4-CIS-DIENE

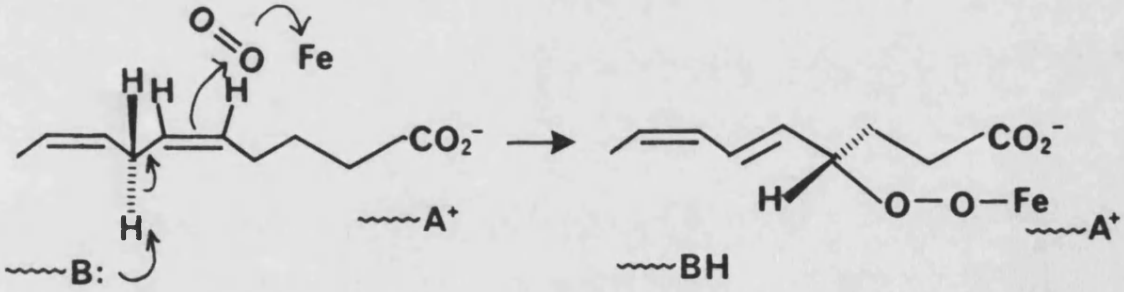




5-HYDROPEROXY PENT
-1-CIS-3-TRANS-DIENE

Scheme 1 MODE OF ACTION OF LIPOXYGENASE

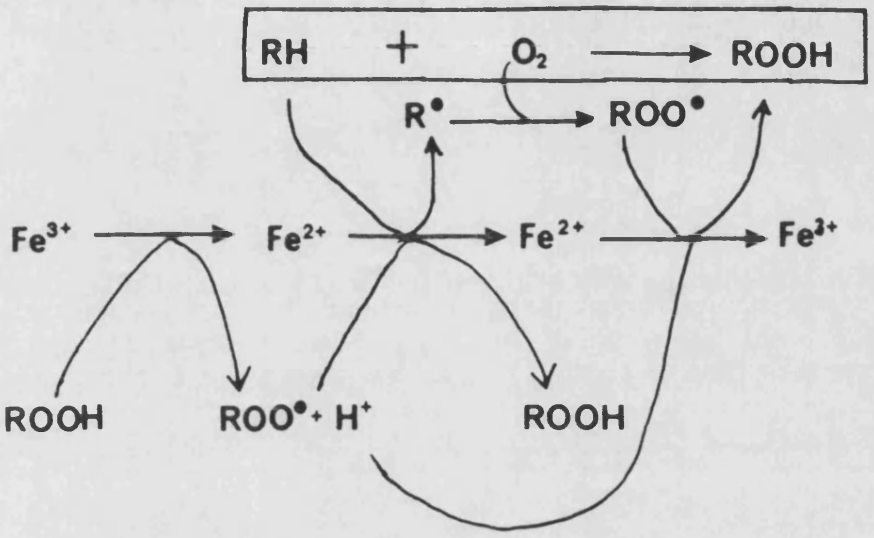
in formation of an activated form of the pentadiene which is susceptible to attack by molecular oxygen across either of the double bonds. The resulting hydroperoxides each contain one cis and one trans double bond separated by a carbon-carbon single bond. Arachidonic acid contains three overlapping cis,cis,1,4 pentadiene moieties and autooxidation gives rise to a mixture of six different hydroperoxides. As the process is non-enzymic each of the hydroperoxides is a mixture of stereoisomers containing the R and S enantiomers. Lipoxygenase-catalysed hydroperoxidation, on the other hand, is characterized not only by positional specificity, but also by specific formation of one enantiomer. Also, a lot of information has been obtained from the model for the cyclooxygenase enzyme.[2]



Mechanism lipoxygenase (Scheme 2)

Lands and Hemler[3,4] suggested electron transfer as a mechanism of generating radical intermediates without cleavage of the hydroperoxide 0-0 bond. Thus the initiating event would be a hydroperoxide of Fe^{3+} to Fe^{2+}

with the concomitant generation of the hydroperoxide radical leading to free radical chain reaction with the substrate. The ability of iron to transfer or accept an electron is of critical importance to lipoxygenase activity.

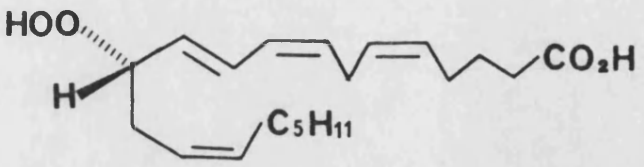


HELMER AND LANDS (1980)

An important characteristic of the lipoxygenase enzyme is the fact that it is activated by its own product (the hydroperoxide).[5]

Several animal lipoxygenases have been isolated and characterised by their positional specificity, and the position(s) of oxygenation commonly identified relative to the carboxy group of the substrate.

12-HPTE(12-hydroperoxyeicosatetrenoic acid)(2) was the first example of a lipoxygenase-derived product in a mammalian system.[6]



12-HPETE (2)

Prior to this lipoxygenase had only been found in plant tissues. The enzyme is widespread and has been identified in peas, potatoes, flaxseed and algae[7]. The positional specificity depending on source or origin.

The birth of mammalian lipoxygenase derived products came with the recognition of "slow reacting substances" as biological factors in 1938 by Feldberg and Kellaway[8]. They found that during perfusion of guinea pig or cat lungs, treatment with cobra venom led to the appearance of what they called "slow reacting substance" (SRS) in the effluent, so called SRS because it had the ability to produce a slow and prolonged contraction of smooth muscle preparations.

Kellaway and Trethewie[9] then discovered a pharmacologically similar substance in the effluent of immunologically sensitized guinea pig lungs treated with a specific antigen in vitro. Some time later Brocklehurst at Eli Lilly laboratories[10,11] demonstrated that in an anaphylatic event materials are generated which showed biological activity similar to Feldberg and Kellaway's SRS.

He was not able to ascertain whether the anaphylatic material and the previously described SRS were the same or different substances, so he modified the acronym to SRS-A to indicate the former. It is now known that these substances are indeed the same.

A major milestone was the discovery that arachidonic acid (A.A.) is the starting point for the synthesis of SRS. Parker and Kakschik[12] came to this conclusion as did Bach[13], who showed, for example, that labelled arachidonic acid becomes incorporated into SRS.

The development that initiated the greatest advance was the discovery in 1979 by Murphy, Hammarström and Samuelsson[14] that the long known very elusive "slow reacting substance of anaphylaxis" (SRS-A) was in fact a product of the mammalian lipoxygenase pathway of the arachidonic acid metabolism. Although SRS activity had been recognised as early as 1938, purification had not been possible until 1976. A considerable help was the use of reverse phase high performance liquid chromatography in the isolation procedure.[15] Evidence from hydrogenation, oxidation experiments, and some physiochemical properties, led Brocklehurst to suggest SRS-A was an unsaturated fatty acid.[16] The U.V. spectrum of SRS-A has a characteristic λ_{max}^{MeOH} at 280nm. This was attributed to a triple conjugated chromophore[17] after the inspection of U.V. spectra of certain well-characterised hydroxylated lipids.[18]

1.1.1 Structure Determination and Biosynthesis

The structures were determined by classical analytical techniques coupled with total synthesis. Reductive desulphurization of SRS with Raney nickel gave 5-hydroxyarachidonic acid indicating a 5-hydroxy function and confirmed the presence of a thio ether linkage.[14] Positions of the double bonds were determined in two ways. Firstly, reductive ozonylsis led to hexan-1-ol demonstrating retention of the Δ^{14} double bond of the precursor.[14] The position of the triene system was located enzymatically by hydroperoxidation with soya bean lipoxygenase.[19] This enzyme was specific for oxygenating C_6 of fatty acids containing a cis,cis 1,4 diene system with concomitant isomerisation of the double bond.[20] The observed shift of 30nm in the U.V. spectrum of the product suggested that oxygenation and isomerisation of a Z-alkene unit at C_{14} had occurred to bring it into conjugation with a pre-existing triene unit. This indicated the presence of a second cis double bond at C_{11} and additional double bonds at C_7 and C_9.

In parallel studies, other research groups were investigating the metabolism of arachidonic acid in rabbit peritoneal polymorphonuclear leukocytes (PMNL). Borgeat incubated arachidonic acid with PMNL and characterised the major metabolite, 5(S)-hydroxyeicosa-6,8,11,14-tetrenoic acid (5-HETE(3)).[2] The formation of the metabolite was not inhibited by indomethacin thereby indicating prostaglandin synthetase enzymes were not

involved. A novel lipoxygenase type reaction was invoked with enzymatic reduction of the first formed hydroperoxide yielding the observed product. Subsequently the same research group isolated another metabolite, 5(S), 12(R)-dihydroxy-6,8,10,14-eicosatetrenoic acid (4). The geometry around the double bonds was ambiguous from spectroscopic data,[22] but was later shown to be 6Z,8E,10E,14Z by chemical synthesis by Corey et al.[23] It was subsequently named leukotriene B_4 (LTB_4).[24] A number of minor metabolites were also characterised,[25] two 5,6-dihydroxy 7,9 11,14 eicosatetrenoic acids (epimers at C_6) and two geometric isomers of leukotriene B_4.

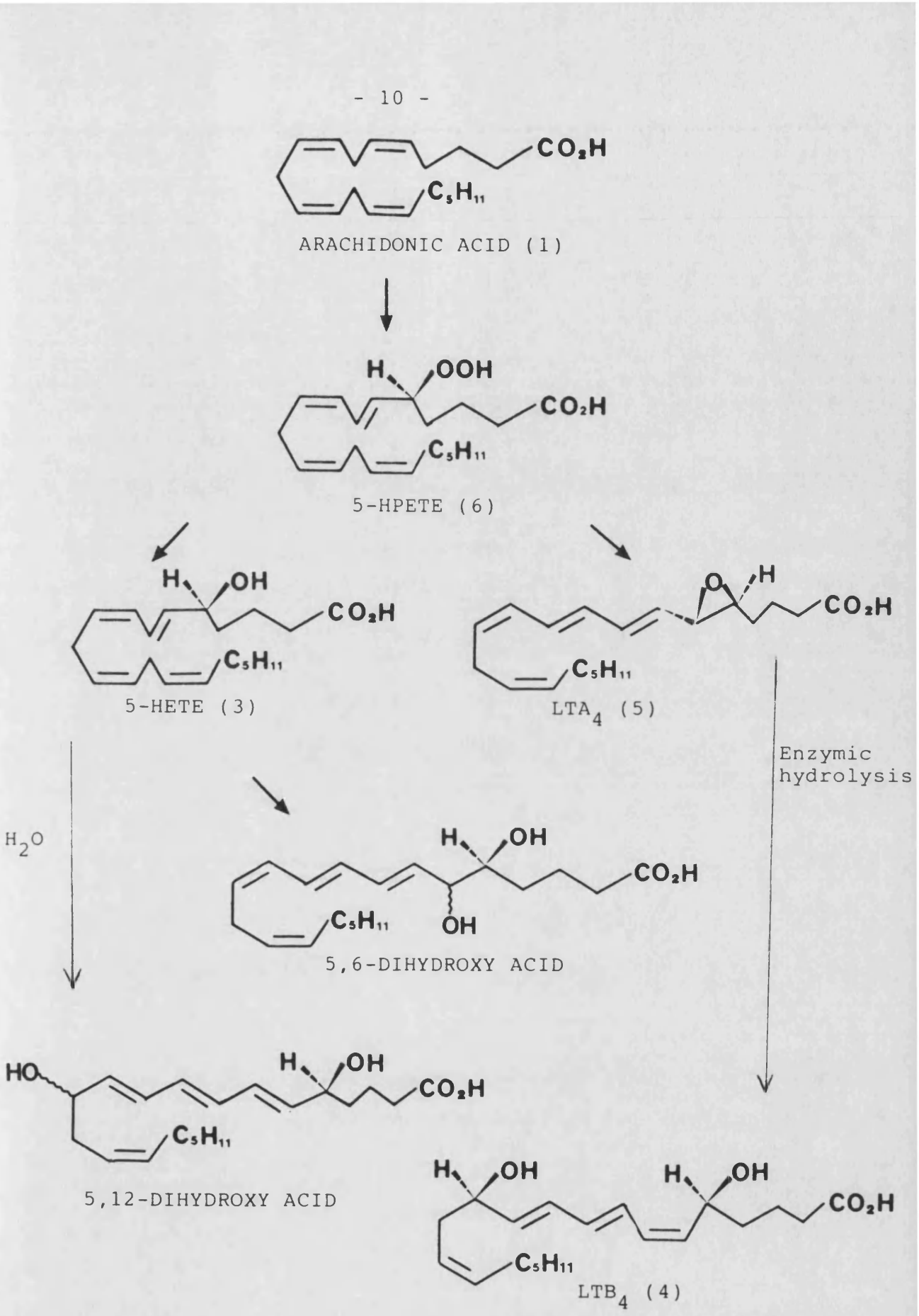
A note on nomenclature is in order here: leukotrienes A-F are referred to as LTX_4 where LT refers to the leukotriene and X denotes the specific leukotriene: LTA_4 is the triene 5(S), 6(S)-epoxide(5) and LTB_4(4) the enzymatic hydrolysis product of LTA_4(5). LTC_4(7), D_4(8), E_4(9) and F_4(10) refer to the peptidoleukotrienes which adorn the fatty acid chain through a cysteinyl sulphide linkage at C_6. The subscript "4" refers to the total number of double bonds in the C_{20} chain.

The structural similarities of the metabolites of arachidonic acid derived from PMNL suggested a common biosynthetic pathway. Samuelsson did some ^{18}O labelling studies where it could be demonstrated that the oxygen of the hydroxy group at C-5 originated from atmospheric O_2, whereas the oxygen of the hydroxy group at C-12 was derived from water.[26] From these observations,

Samuelsson and Borgeat postulated that the leukocytes generated an unstable intermediate which could undergo attack by water, alcohols and other nucleophiles. The intermediate was shown to be very labile at low pH with a short half-life (approx 3 min at pH 7.4 at 37^{o}). Studies showed that LTB_4 was produced enzymatically, whereas the other metabolites present were the result of non-enzymatic hydrolysis. From these results Samuelsson proposed the intermediate 5(S), 6(S)-epoxide (LTA_4); the structure was confirmed by Corey et al's synthesis of this intermediate.[27] This epoxide could be transferred by neutrophils into leukotriene B_4. From the following results, Samuelsson proposed that the transformation of arachidonic acid in PMNL occurs according to Scheme 3.

It was becoming apparent from a number of sources that the slow reacting substances were in fact related to the newly discovered leukotrienes. They were both metabolites of arachidonic acid.[12,21] The biosynthesis of 5-HPTE[22] and that of SRS-A[29] was not inhibited by indomethacin and the calcium ionophore A23187 stimulated the production of both SRS[30] and leukotrienes[31] from arachidonic acid.

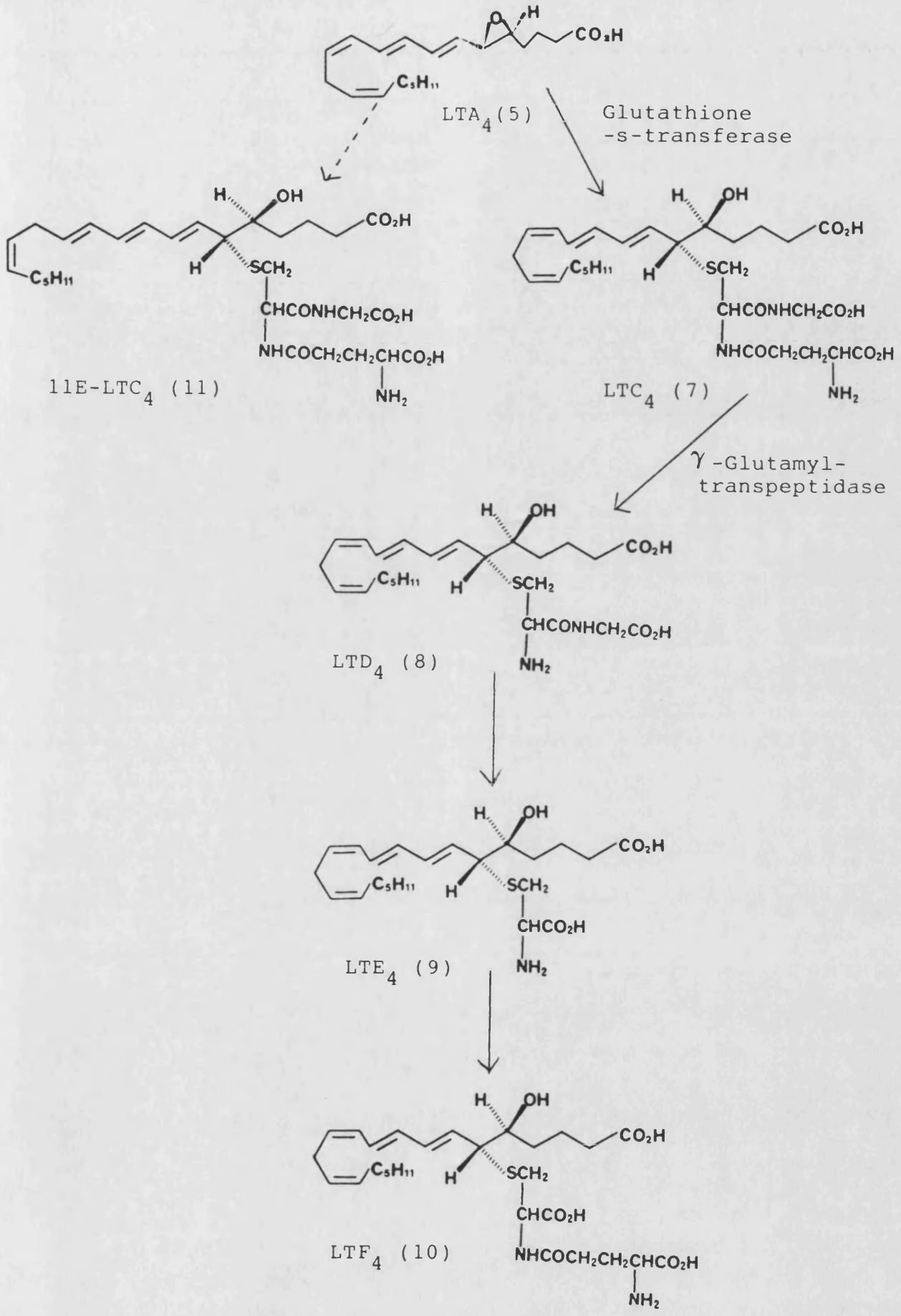
It soon became evident that SRS was a conjugate of LTA_4(5) and a cysteine containing moiety. Incubation of mouse mastocytoma cells with arachidonic acid, cysteine and ionophore A23187 gave, as the major component, SRS having a U.V. spectrum characteristic of a leukotriene.[14] Therefore SRS was apparently a derivative of 5-HETE (3)


ARACHIDONIC ACID (1)
5-HPETE (6)
5-HETE (3)
LTA4 (5)
Enzymic hydrolysis
H2O
5,6-DIHYDROXY ACID
5,12-DIHYDROXY ACID
LTB4 (4)

Scheme 3

with a cysteinyl containing substituent. Determination of the substituent by amino acid analysis showed that it was glutathione (ψ-glutamylcysteinylglycine) residue. Reaction of enatiomerically pure LTA_4 with gluthione yielded a product whose chemical, physical and biological properties closely resembled SRS isolated from mouse mastocytoma cells.[32] This was the first published structural determination of a slow reacting substance, 5(S)-hydroxy-6(R)-S-glutathionyleicosa-7E,9E,11Z,14Z-tetrenoic acid (LTC_4(7)). In addition to LTC_4, small amounts of another substance were present, this was found to be the 11-E isomer of LTC_4(11),[33] the bio-synthetic pathway for this is not known.

Two groups of workers also established the structure of the slow reacting substance released by rat basophil leukaemia cells (RBL-1).[34,35,36] RBL-1-SRS, was given the trivial name leukotriene D_4 and was shown to be 5(S)-hydroxy-6(R)-cysteinylglycinyleicosa-7E,9E,11Z,14Z-tetrenoic acid (8). It was also shown that ψ-glutamyltrans peptidase catalysed the conversion of LTC_4 into LTD_4 indicating that LTC_4 was an intermediate in the bio-synthesis of LTD_4.[36] The 6-cysteinyl conjugate was identified in SRS-A released from rat peritoneum,[37] its structure and stereochemistry was confirmed by chemical synthesis[38] and was found to be 5(S)-hydroxy-6(R)-cysteinyleicosa 7E,9E,11Z,14Z tetrenoic acid (9) and was assigned the name leukotriene E_4 (9). LTF_4 (10) has been synthesised chemically, but as of yet has not been shown to be a natural product.


LTA4 (5)
Glutathione
-s-transferase
11E-LTC4 (11)
LTC4 (7)
γ-Glutamyl-
transpeptidase
LTD4 (8)
LTE4 (9)
LTF4 (10)

Scheme 4

The biosynthetic pathway of leukotrienes C_4, D_4 and E is shown in Scheme 4, also the structure of leukotriene F_4.

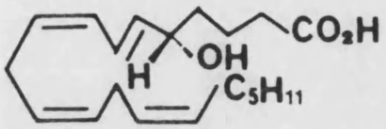
Evidence for this proposed scheme comes from the following:- Biosynthesis of LTC_4 from LTA_4 has been observed,[40] as has the enzymatic removal of the ψ-glutamyl residue from LTC_4 to form LTD_4.[32] LTE_4 has been formed from LTD_4 using an aminopeptidase component of a particular arylsulphatase.[41]

Leukotrienes are transformed via a metabolic cascade; therefore it was not surprising that the relative amounts of LTC_4, LTD_4 and LTE_4 found were dependent on the source of stimulus and type of cell.[42]

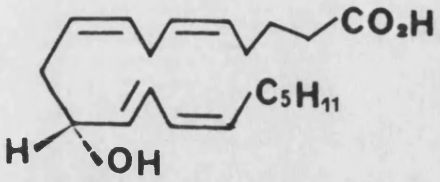
Samuelsson proposed that the single defined compounds be known as the relevant leukotriene, and that SRS describes biologically derived material, where the ratios of leukotrienes are unknown.

Leukotriene formation is not restricted to products derived from 5-HPETE. Arachidonic acid can produce six different monhydroxylated metabolites via a lipoxygenase pathway. See Scheme 5.

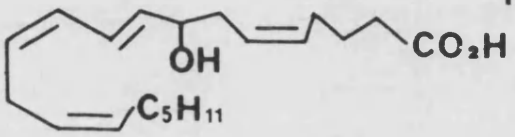
Indeed, two isomers of 14,15-dihydroxyeicosa-5,8,10, 12-tetrenoic acid (14-15-LTB_4) (17) and two isomers of 8,15-dihydroxy-eicosa-5,9,11,13-tetrenoic acid (8-15-LTB_4) (16)were isolated from incubation of arachidonic acid with human leukocytes,[43] (Scheme 6) which are believed to arise from the intermediate 14,15-LTA_4(15). Another important pathway yields 12-HPETE in platelets and lymphocytes.[44,45]



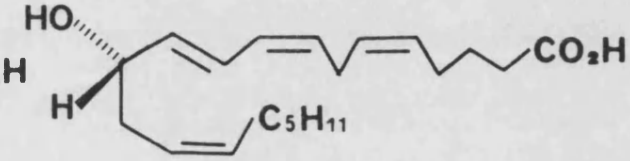
5-HETE (3)



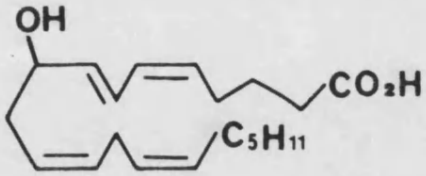
11-HETE



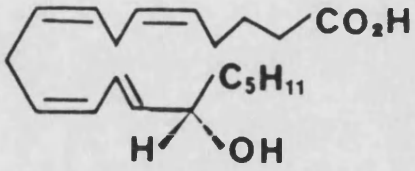
8-HETE



12-HETE (12)

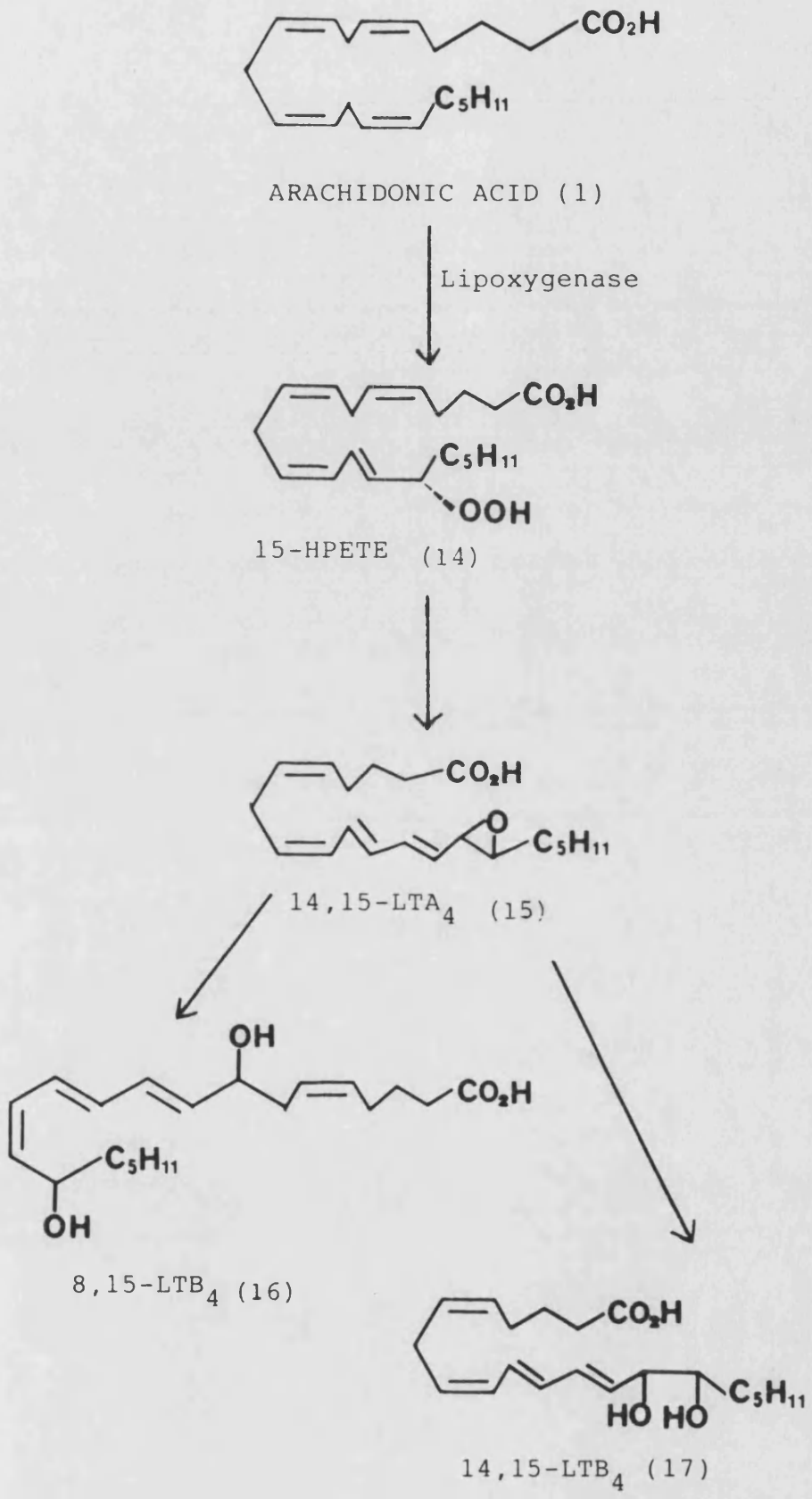


9-HETE



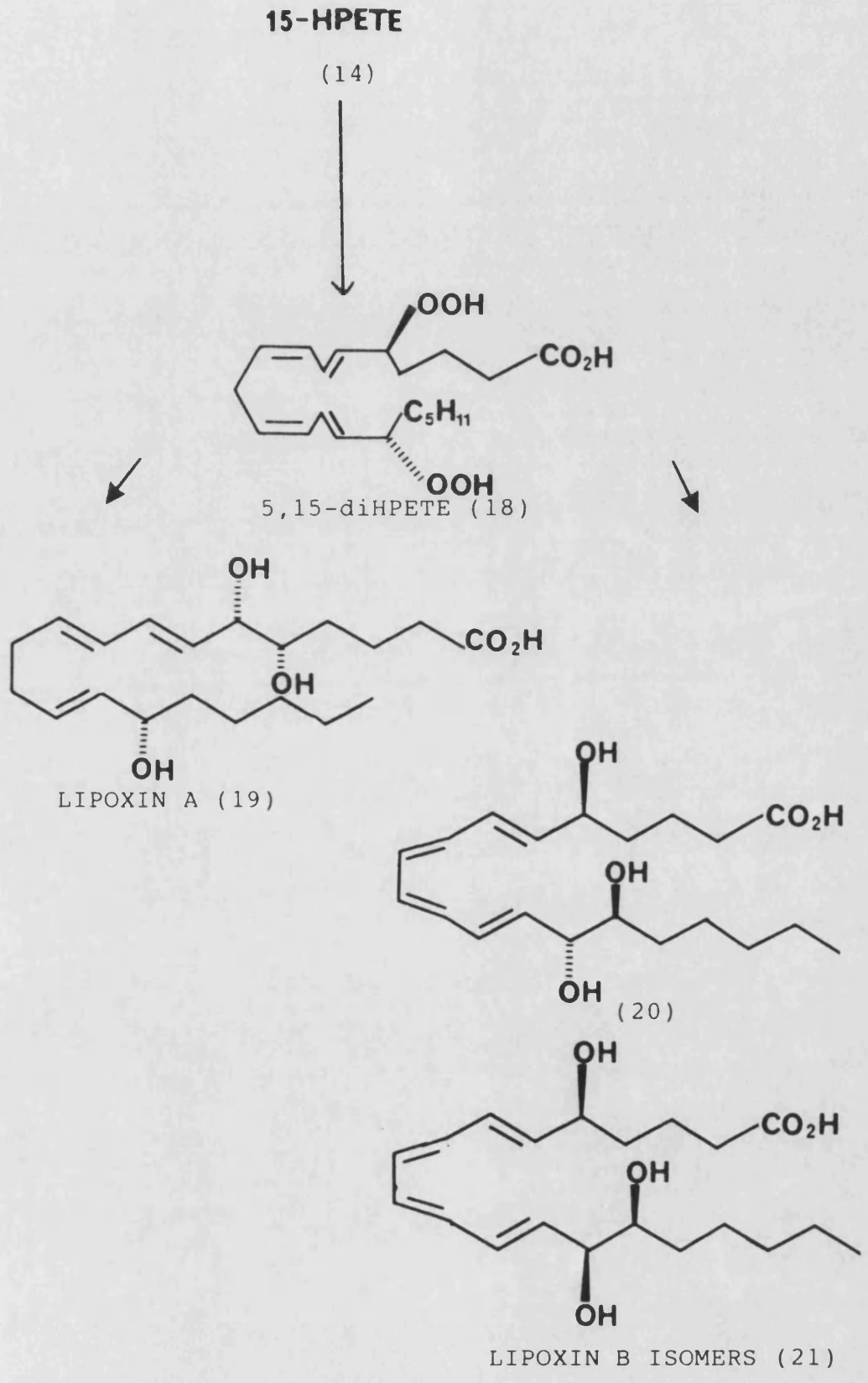
15-HETE (13)

Scheme 5: HYDROXY EICOSATETRENOIC ACIDS (HETEs)



Scheme 6: PROPOSED PATHWAY OF 15-LIPOXYGENASE

Recently, arachidonic acid has been shown to give a new class of oxidative metabolites the so called lipoxins. The lipoxins were first reported by Samuelsson and co-workers,[46,47] who incubated 15-HPETE(14) with purified human leukocytes, which gave rise to lipoxins A and B, two isomeric conjugated trihydroxytetraenes. Their structures are shown overleaf.[48] (Scheme 7).

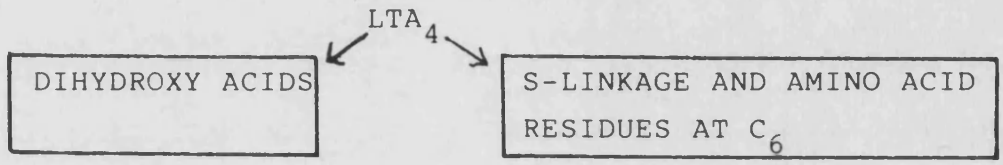

15-HPETE
(14)
OOH
CO2H
C5H11
OOH
5,15-diHPETE (18)
OH
CO2H
OH
OH
LIPOXIN A (19)
OH
CO2H
OH
OH
(20)
OH
CO2H
OH
OH
LIPOXIN B ISOMERS (21)

Scheme 7

1.2 Pharmacology

1.2.1 Introduction

Leukotrienes are potent mediators of allergic, inflammatory and other pathologic events. Their biological action may be divided into two groups: those involving contraction of smooth muscle (as exhibited by the sulphidopeptide leukotrienes) and those involving chemotaxis as exhibited by dihydroxy acids (such as LTB_4 and its isomers).



LTB_4 AND ISOMERS	LTC_4, LTD_4, LTE_4
Chemotaxis	Contraction of smooth muscle
Chemokinesis	Bronchoconstriction
Aggregation of PMNS	Vascoconstriction
Exudation of plasma	Exudation of plasma
Contraction of guinea pig parenchyma	Stimulation of phospholipase (guinea pig lung)

Summary of leukotriene actions

Various inflammatory cells including leukocytes,[49,50] eosinophils,[51,52] macrophages,[53,54] and mast cells[55,56] in several species including humans, produce leukotrienes from either added AA or from endogenous AA in the presence of specific stimulants such as the chemotactic peptide, F-met-leu-Phe,[57] platelet-activating factor (PAF),[58]

phorbol myristyl acetate (PMA)[59] and IgE directed antigens.[60,61] Leukotrienes then produce a physiological response by interacting with specific, high affinity receptors.

Leukotrienes are produced by cells (PMNs and macrophages) that are present in large numbers at inflammatory sites.[62] If stimulated with the calcium ionophore A-23187, PMNs produce LTB_4, which has potent chemokinetic activity and is also an aggregating agent for neutrophils.[63] LTB_4 is one of the most important chemotactic factors known.

The role of LTB_4 as an inflammatory mediator is supported by studies showing high amounts of LTB_4 in the skin chamber fluid of involved skin from psoriatics[64] and in gouty effusions.[65] Leukotrienes may also be involved in the modulation of pain in inflammatory conditions. However, the mechanism of action of response is not fully understood.

Leukotrienes C_4, D_4 and E_4 may also be important mediators of inflammatory processes. LTD_4 and LTE_4 influence vasopermeability in guinea pig skin and their activities are potentiated by the presence of prostagladin vasodilators.[66] Also, LTC_4 and LTD_4 increase neutrophil adherence and may also affect release reactions of macrophages.[67]

Samples of tissue from inflamed sites contain high levels of LTB_4[68] and also have increased ability to synthesise 5-lipoxygenase products compared with normal

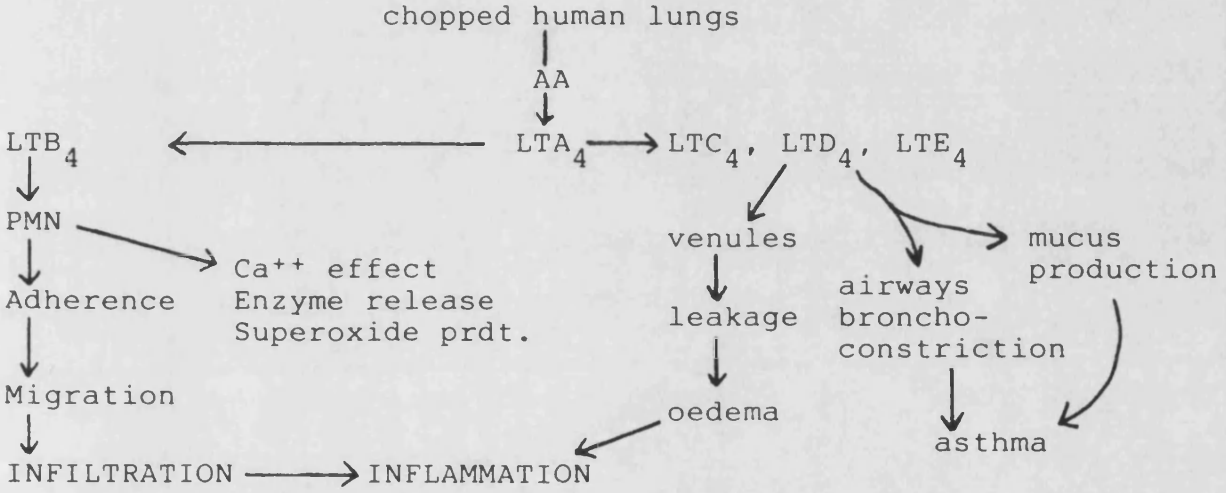
tissue. Synovial fluids from rheumatoid arthritic or gouty patients also contain large numbers of neutrophils and elevated levels of LTB_4.[62,65]

In the normal immune response, antibodies are produced which neutralise antigens present without any ill effect in the host. In hypersensitivity something evidently goes wrong with the normal immune response. The combination of antigen with antibody triggers a poorly controlled excessive response and this causes the release of various mediators which tend to exacerbate the situation. These mediators serve as the immediate cause of pathological change. The extreme form of hypersensitivity is called anaphylaxis and is derived from the Greek words meaning "against protection".[69] The major mediators released can be subdivided into two groups: (1) Preformed mediators (already present in the mast cell granules before stimulation and released within seconds, which include histamine) and (2) newly synthesised mediators (not detected before stimulation, but rapidly synthesised, and then released a few minutes after antigenic challenge); these include the leukotrienes and "platelet activating factor". In addition, it is probable that prostagladins are also released in such reactions.

The physiological actions of the primary metabolite 12-HPETE and the corresponding alcohol 12-HETE is unclear, although 12-HPETE is believed to stimulate leukotriene biosynthesis in human blood leukocytes.[70] Consequently, it has been concluded that leukocyte lipoxygenase products

of arachidonic acid have the capacity to amplify the cellular component of inflammatory reactions.[71] HPETE and HETE have additionally been implicated as possible endogenous regulators of prostacylin (PGI_2) biosynthesis, thus perhaps serving a physiological role in the regulation of vascular tone.[72]

The physiological effects of the leukotrienes is shown diagrammatically below:



Scheme 8

1.2.2 Interactions between the lipoxygenases

There are a number of interactions between the various dioxygenases involved in the metabolism of AA and many of these may be biologically significant. As well as the inhibitory effect of 15-HPETE on PGI_2 synthesis,[73] it has been suggested that generation of hydroperoxy and hydroxy acids may be important in biochemically regulating the synthesis of leukotrienes.

It seems likely that C-15 and C-12 lipoxygenases exert, respectively, inhibitory and stimulating influences on the synthesis of leukotrienes in leukocytes.[74,75] The finding that 12-HPETE has a stimulating effect on the activity of 5-lipoxygenase brings additional support to the hypothetical role of 15-HETE.[76] The biological significance of the 5S,12S-DiHETE's remains unclear; it might be regarded as a product reflecting the stimulating interaction of 12-HPETE with the C-5 lipoxygenase. Due to these interactions, when considering the biochemical mechanisms involved in allergy and inflammation it is important to ascertain the biological importance of the inhibitory and stimulating effect of hydroxy and hydroperoxy acids in leukotriene synthesis.

One of the most important areas of development is to ascertain what are the crucial differences between the normal and diseased state immune response. A successful resolution of this problem would help the treatment of a large number of human diseases including asthma, allergy and other forms of hypersensitivity which affect an estimated fifth of the world's population.

1.3 Lipoxygenase inhibitors

1.3.1 Introduction

There are a number of points of intersection in the arachidonic acid cascade, where inhibition may prove clinically useful in the treatment of asthmatic and inflammatory conditions. The point of intersection in our case is the lipoxygenase catalysed addition of oxygen to arachidonic acid giving the HPETE's and we are particularly interested in the 5- and 12-positions and the design of transition state surrogates as enzyme inhibitors.

1.3.2 Transition state surrogates as enzyme inhibitors

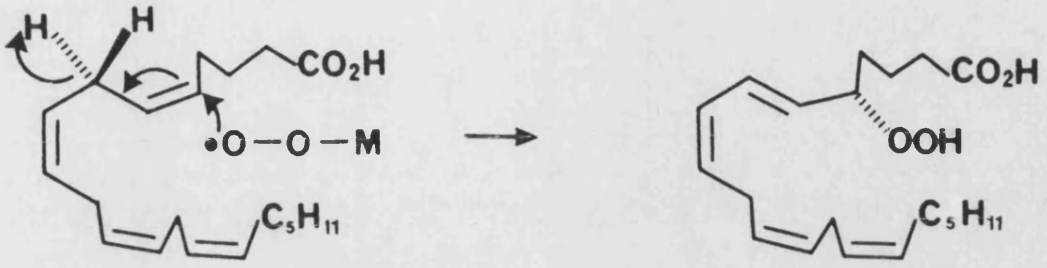
An organic reaction between two types of molecules proceeds through a high energy activated complex known as a transition state. In enzymes, from mathematical analysis of equilibrium constants, the transition state is considered to bind to the enzyme at least 10^{10} times more tightly than the substrate. A transition state surrogate is a stable compound that structurally resembles the unstable transition state of the enzymatic reaction.[77] There are a certain number of factors needed for the design of transition state surrogates: they require a knowledge of mechanism. Bond-breaking and bond-making mechanism should be similar. It is not possible to design a stable compound which mimics transition state closely since transition state is unstable. Why design

transition state surrogates? A transition state surrogate of a substrate reaction would be expected to be sufficiently tightly bound to be an excellent reversible inhibitor. As it binds more strongly to the enzyme than substrate, it should be more useful in therapy than the classical type (which only resembles the substrate). Its action is less likely to be reversed by build up of substrate.

1.3.3 Transition state surrogates for 5- and 12-lipoxygenase

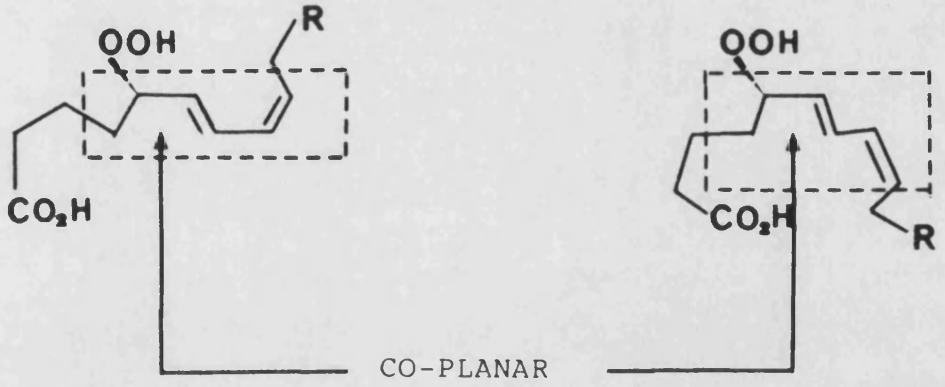
The proposed mechanism for the conversion of arachidonic acid into 5-HPETE is as follows and is based on the analogous first stage of the cyclooxygenase reaction.[2] Arachidonic acid is initially bound to the lipoxygenase via the carboxyl group, and folds on to the enzyme hydrophobic surface, possibly involving a change of conformation to form a hydrophobic 'pocket'. The pro-R-hydrogen at C-7 is abstracted homolytically (as a free radical) from the bottom side of the folded substrate. This is immediately followed by topside allylic addition of molecular oxygen to form the (R)-5-peroxy radical. There is considerable evidence to support a mechanism of this type.[2] (Same applies for the conversion of arachidonic acid into 12-HPETE.)

Proper orbital overlap required co-planarity of atoms 4,5,6,7 and 8. To further weaken the C_7-H bond, the double bonds between atoms 5-6 and 8-9 probably



Scheme 10: Mechanism for conversion of arachidonic acid into 5-HPETE

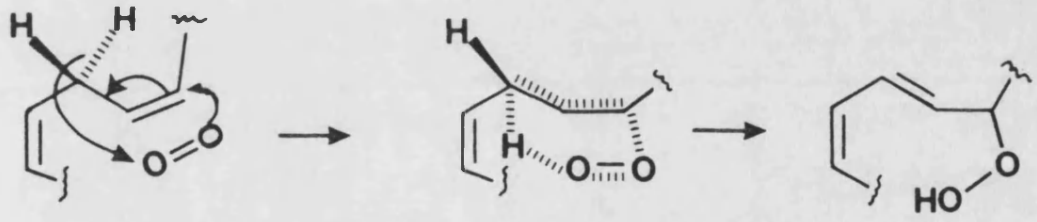
lie in the same plane. These requirements taken together provide two hypothetical conformations of the product, 5-HPETE, in the 5-lipoxygenase active site.[78]



Scheme 11: Proposed conformations of 5-HPETE in the active site of 5-lipoxygenase

From these free radical processes one can envisage the transformation in terms of a cyclic ene reaction involving free radicals containing a six-membered

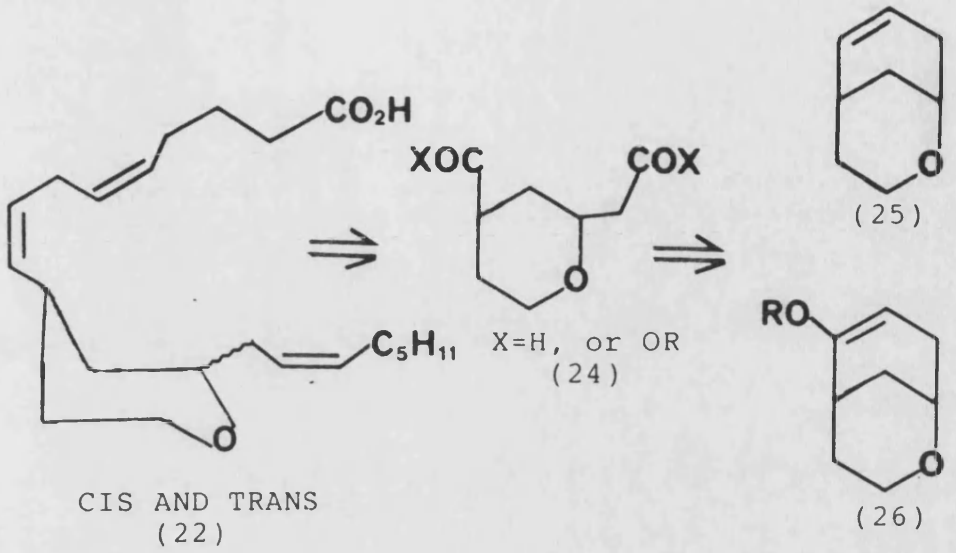
transition state. The proposed transition state contains oxygens in the 2 and 3 positions and from this were derived compounds such as the cyclic ethers (22 and 23) which depending on the association constant of the enzyme may act as transition state surrogates. Our objective was to synthesise transition state surrogates for critical enzymatic steps in the synthesis of leukotrienes and 12-HETE in order that transition state requirements for these processes may accurately be defined.

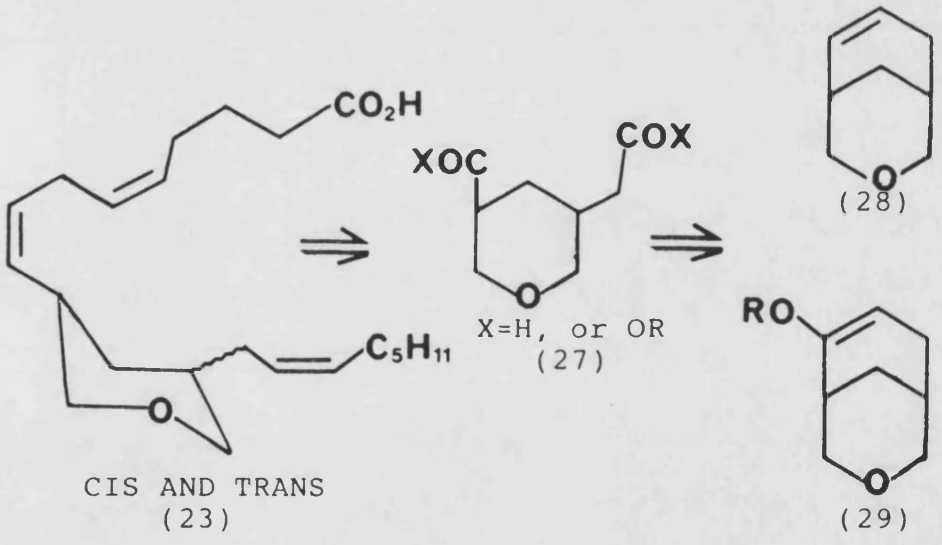


Scheme 12: Proposed cyclic ene reaction

1.3.4 Retrosynthetic Analysis

Retrosynthetic analysis shows that the target surrogates are accessible from the (2)-3-oxabicyclo [3.3.1]non-6-enes (25 and 28) and the corresponding enol ethers (26 and 29), all of which are unknown. It was envisaged that the (2)-(3)-oxabicyclo[3.3.1]nonenes would be ozonylsed and then selective Wittig reactions would be performed to elaborate the side chains. This was the basic synthetic plan.



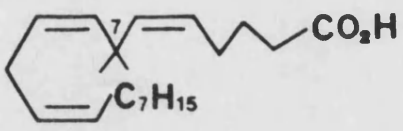


Scheme 13: RETROSYNTHETIC ANALYSIS

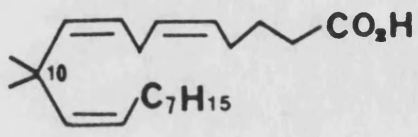
1.3.5 Review of lipoxygenase inhibitors

The discovery of the leukotrienes and the elucidation of the biosynthesis of these mediators of inflammatory and allergic disorders has presented synthetic chemists with the opportunity of preparing analogues of the biochemical intermediates that may act as inhibitors of the enzyme. This review is going to be concerned only with inhibitors that bear some structural resemblance to AA or HETE's, i.e. substrate analogues.

A variety of substituted arachidonic acids have been identified as selective inhibitors of the lipoxygenase enzyme. Via this pathway, the biosynthesis of leukotrienes is initiated by stereospecific proton abstraction from C-7 of AA. AA analogues have been designed to function as inhibitors by blockade of proton abstraction from C-7, C-10 and C-13. This has been done in a number of ways by insertion of a gem-dimethyl.[78,79,80] Perchonock et al[78] synthesised 7,7-dimethyleicosa-5(Z), 8(Z), 11(Z)-trienoic acid (30) and its 10,10-dimethyl isomer (31) in which the



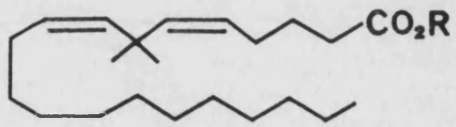
(30)



(31)

biochemically reactive positions 7 and 10 have been blocked by a gem-dimethyl. This choice of trienes rather than the tetraenes was based on the assumption that, lacking the 14,15-double bond, they would not be suitable as substrates for the cyclooxygenase pathway of the AA metabolism. The effect of compounds (30) and (31) on AA metabolism in RBL-1 cells was that (30) inhibited the formation of 5-lipoxygenase products 5-HETE and 5,12-di-HETE by 50%, as well as the cyclo-oxygenase product PGD_2 by 30-40%. Compound (31) was more selective for the 5-lipoxygenase pathway, inhibiting the formation of 5-HETE and 5,12-di-HETE by 40% at 100μm, while having little inhibitory activity on the formation of PGD_2.

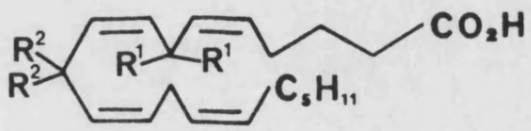
Using similar reasoning to Perchonock et al[78], that a gem dimethyl group would prevent proton abstraction at C-7, F Scheinman et al[79] undertook the synthesis of 7,7-dimethyl-eicosa-5(Z), 8(Z)-dienoic acid (32) and its methyl ester (33).



(32) R=H
(33) R=CH_3

By omitting olefinic linkages at carbons 11-12 and 14-15, it was anticipated that they would not be in competition with arachidonic acid for binding to the active site of 12-lipoxygenase or cyclooxygenase and would thus be selective inhibitors of 5-lipoxygenase. Acid (32) at 50μm inhibited 5-lipoxygenase from RBL-1 cells[81] and human PNN leukocytes[82] by 43% and 26% respectively. Ester (33) was more active, giving inhibition of 74% and 50% at 50μm. Both compounds were selective in their actions.

Pfister and Murthy[80] synthesised 7,7-Me_2-AA (34) and 10,10-Me_2-AA (35). These were chosen as potential inhibitors as (34) could block the formation of 5-HPETE from AA (a double bond shift from 5-6 to the 6-7 position is unlikely because C-7 in (34) is tetrasubstituted) whereas (35) might inhibit the conversion of 5-HPETE to LTA_4 as there are no abstractable protons at C-10.

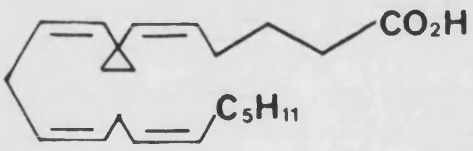


(34) R^1=Me, R^2=H
(35) R^1=H, R^2=Me

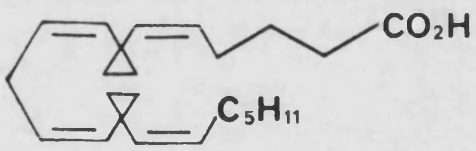
The biological data for these compounds was somewhat contradictory. However, it is somewhat difficult to compare inhibitors as in many cases testing methods used are very different. A paper published in

Prostaglandins (1984) by Cohen, Weber, Banner et al.[83] who investigated the biological activity of these dimethyl AA's in great detail found that although these compounds did indeed block the ionophore-induced production of SRS-A from rat peritoneal cells, their mechanism of action does not appear to involve the inhibition of 5-lipoxygenase even in those compounds that were designed to block initial proton abstraction at the C-7 position. The actual mode of inhibition is not fully understood.

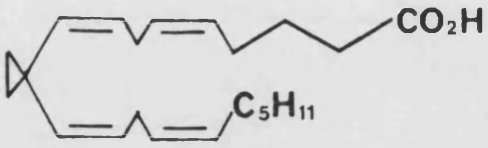
Another way designed to prevent proton abstraction was by the use of cyclopropane derivatives. The cyclopropane group has been inserted at various points and consequently has had quite different effects on activity.



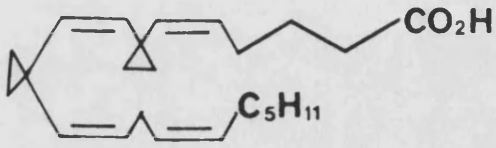
7-EAA (36)



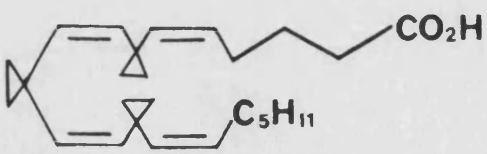
7,13-DEAA (37)



10-EAA (38)



7,10-DEAA (39)

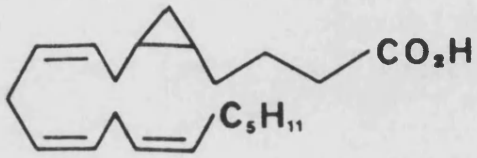


7,10,13-TEAA (40)

EAA=Ethanoarachidonic acid
DEAA=Diethanoarachidonic acid
TEAA=Triethanoarachidonic acid

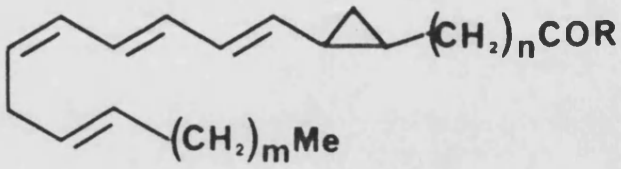
i.e. in between a net of double bonds where only two of the analogues showed minor biological activity, these were 7,13 DEAA (37) and 7,10,13-TEAA (40).

Also, by replacement of a double bond,[86] as in 5,6-methano-AA (41), however this was inactive.



(41)

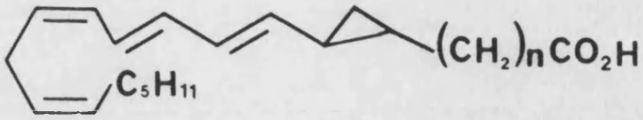
K.C. Nicolaou et al[87] prepared 5,6-methanoleukotriene A_4 (42) and 4 of these derivatives inhibited 5-lipoxygenase activity in cloned mastocytoma cells.



(42)

n=2,3 or 4, M=3,4 or 5, R=OM (where M is a pharmaceutically acceptable cation).

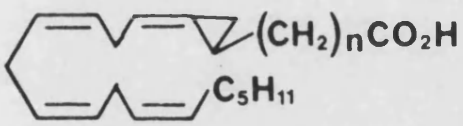
Toda et al[84] also prepared similar compounds (43).



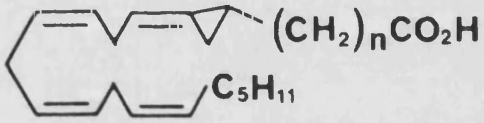
(43) n=1, 3 or 4

The n=3 compound selectively inhibited 5-lipoxygenase activity without inhibiting the cyclooxygenase and 12-lipoxygenase pathways in guinea pig and rabbit platelets.[84]

Raf. N. Misra prepared methylene cyclopropane analogues of arachidonic acid.[88] It was hoped that (44) and (45) would act as conformationally-restricted analogues



(44) n=1,2

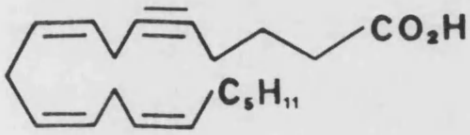


(45) n=1,2

of AA which specify the orientation about the 5,6-double bond of the C1-C4 carboxyl side chain relative to the aliphatic position of the molecule. He postulated that the methylene cyclopropane analogue best able to mimic the reactive conformation of the natural substance would be the most effective inhibitor. However, no biological

activities were reported.

Acetylene analogues of AA have been synthesised with the aim of inhibiting lipoxygenase. These analogues contain triple bonds in the place of double bonds, so that hydrogen abstraction and subsequent peroxidation cannot occur.



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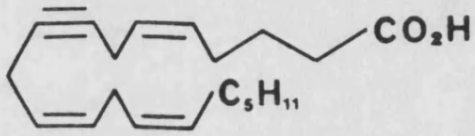

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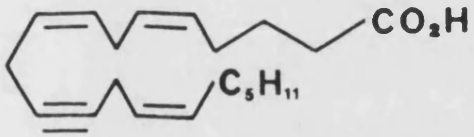

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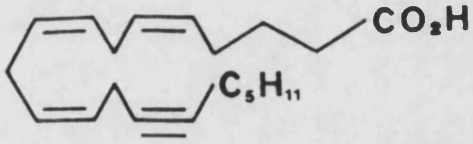
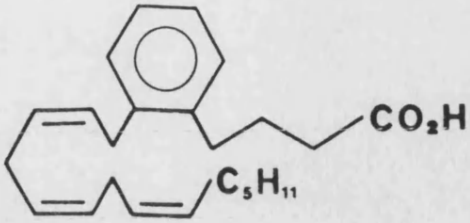


(49)

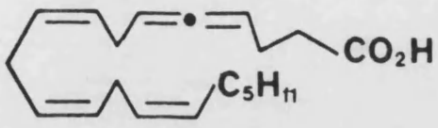
The 5-6, 8-9, 11-12 or 14-15-dehydroarachidonic acid (46, 47, 48, 49) selectively block peroxidation in the 5, 11 or 15 positions respectively.[89,90,91] Another solution to this problem was the 5,6-benzo-AA (50)[84], where the double bond shift from the 5-6 to the 6-7 position would involve deconjugation of the benzene ring which is unlikely to occur.



(50)

5,6-benzo-AA (50) was shown to inhibit the formation of 5-HETE and LTB_4 from intact human PMN's.[84]

An irreversible inhibition of the LT pathway was observed with the allenic 4,5-dehydro-AA (51) in RBL cells.[92] It was found to have the same inhibitory activity as eicosa-5,8,11,14-tetraynoic acid (ETYNA) (52) toward the formation of LTB_4 and was twice as potent as ETYNA toward the formation of 5-HETE using intact PMN's.[93]



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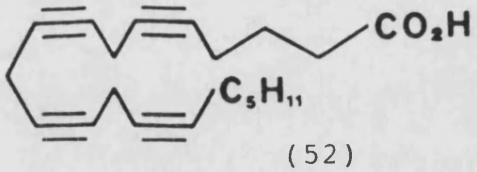
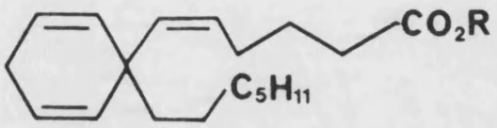
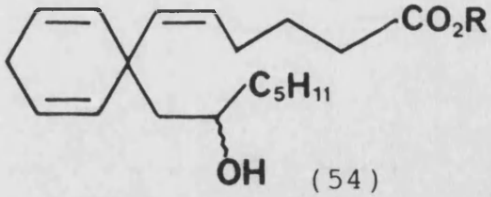


(52)

Sipio created his quaternary centre at C-7 by use of the spiro-trienes (53) and (54) and he hoped that these would be inhibitors of L.T. biosynthesis.[94]



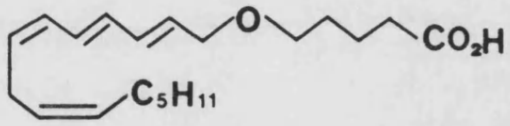
(53)



(54)

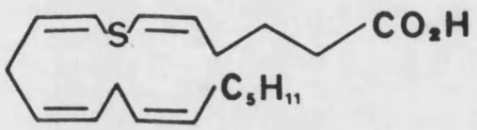
Spiro-triene (53) was found to selectively inhibit 5-lipoxygenase from RBL-1 cells (IC_{50}=120μm) while having a negligible effect on prostaglandin synthetase. Compound (54) was also a selective inhibitor of 5-lipoxygenase (IC_{50}=6μm).

Other approaches to the synthesis of lipoxygenase inhibitors have involved the introduction of hetero-atoms into key positions. The secoleukotriene A_4 (55) causes a decrease in the formation of LTB_4 in human PMN's.[95]

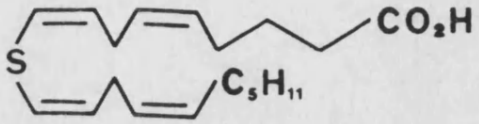


(55)

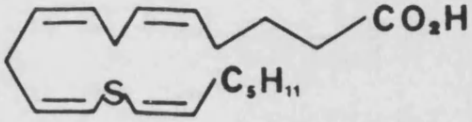
A number of thiaarachidonic acids have also been synthesised. These are the 7-thia (56), 10-thia (57) and 13-thia-AA (58).[96,97]



(56)



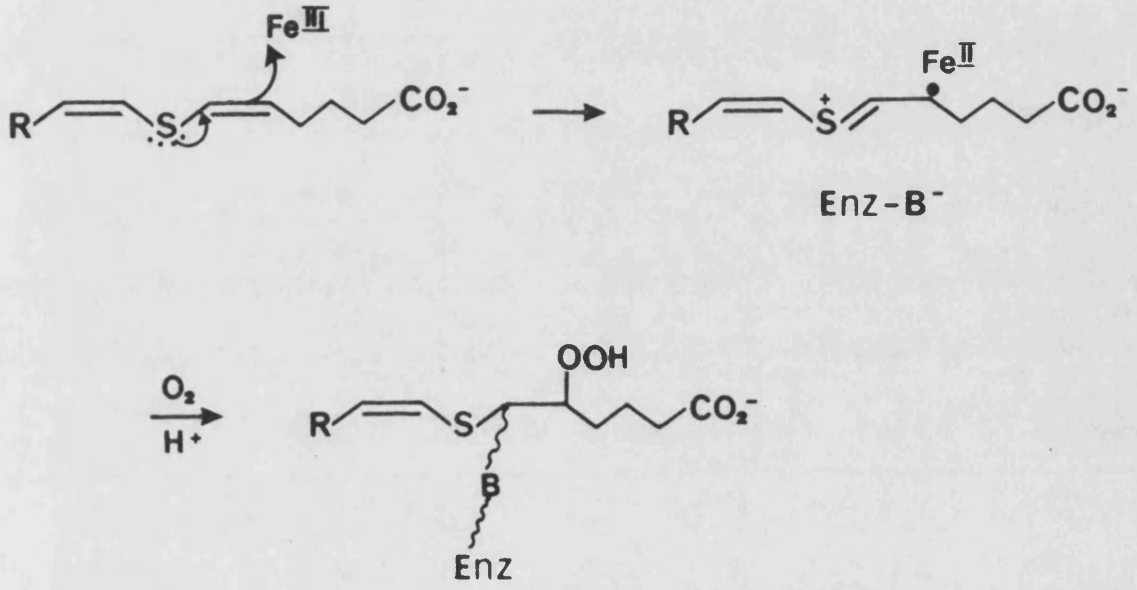
(57)



(58)

The 7-thia AA (56) was found to be an oxygen and time dependent irreversible inhibitor of the 5-lipoxygenase of rat basophilic cells.[96] The 13-thia AA (58) was found to be a time and O_2 dependent irreversible inhibitor of soya bean 15-lipoxygenase enzyme whereas 10-thia AA (57) was found to serve as a good substrate. The reason for the activity of 7-thia AA has been rationalised as follows: Although it contains no abstractable proton, the high-electron donating character of the divinyl sulphide unit can allow direct electron transfer to Fe(III) thereby activating (57) to react with oxygen even in the absence of an abstractable proton. Covalent coupling of enzyme and inhibitor as shown in

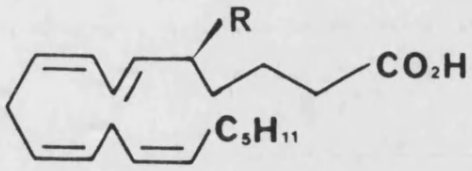
Scheme 14 would lead to irreversible deactivation of the lipoxygenase enzyme.[96]



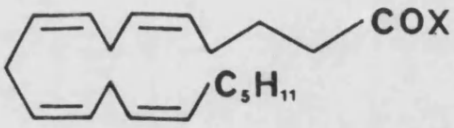
Scheme 14 Mode of inhibition of 7-thia AA

5-hydroxamyl (59) and 5-hydroxamylmethyl-6,8 11,14-eicosatetrenoic acid (60) were also found to be inhibitors of 5-lipoxygenase.[98] They were synthesised to act as iron chelators (as hydroxamic acids are known to be iron chelators[99]) and provide additional binding compared to that of the substrate, arachidonic acid.

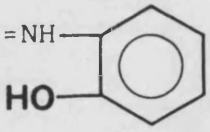
Corey and coworkers,[100] have prepared a number of acid derivatives of AA and a number of them have been shown to be potent, competitive inhibitors of 5-lipoxygenase.



(59) R=CONHOH
(60) R=CH_2CONHOH

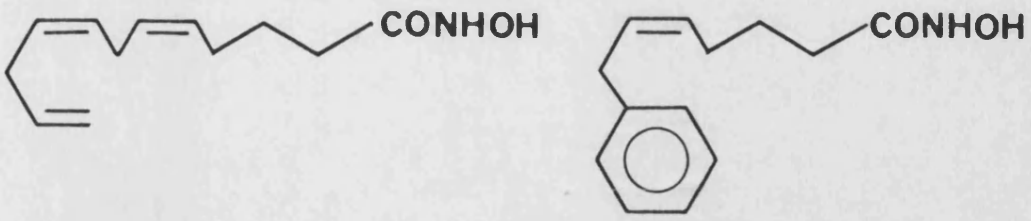


(61) X=NH_2
(62) X=NHOH
(63) X=N(CH_3)OH
(64) X=N(t-Bu)OH
(65) X=NH



The arachidonamide (61) was found to be a competitive inhibitor. All three hydroxamates (62), (63) and (64) were found to be powerful inhibitors of 5-lipoxygenase. The hypothesis for their high potency is that the hydroxamate function in (62), (63) and (64) might be well positioned to coordinate with the catalytically crucial metal ion. They also found that the full eicosanoid chain is not required for strong inhibition as the synthetic hydroxamates (66) and (67) were also good

inhibitors.



(66) (67)

The phenolic arachidonamide (65) was found to be considerably less potent than the hydroxamates (62,63,64).

From the review it can be seen that a number of methods have been used in the attempt to make lipoxygenase inhibitors. The blockade of proton abstraction from C-7, C-10 and C-13 by the use of various groups: gem dimethyl, cyclopropane, benzene and spiro derivatives of arachidonic acid. The use of acetylenic and allenic derivatives so that hydrogen abstraction and subsequent peroxidation cannot occur. Blocking the critical carbon atoms to prevent hydrogen removal is more likely to give inhibitors that are merely competitive fatty acid analogues. Binding covalently seems more likely to have greater biological consequences than would the general competitive hydrophobic binding of a fatty acid to the enzyme.

The introduction of heteroatoms such as oxygen and sulphur into key positions, where in the case of sulphur they act as electron donors and the lone pair allows direct electron transfer. Also, by the use of hydrox-

mates which act as iron chelators (to coordinate with the catalytically crucial metal atom).

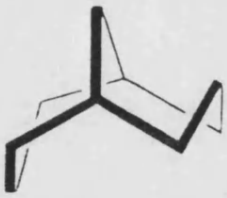
The design and synthesis of lipoxygenase inhibitors has been a rapidly expanding field, which has resulted in greater understanding of the mechanisms evolved. With this greater understanding hopefully in the future it should be possible to design rational inhibitors for any of the lipoxygenases and therefore have selective inhibitors although this by itself may not lead to clinically useful drugs.

2. (2)-3-oxabicyclo[3.3.1]nonanes

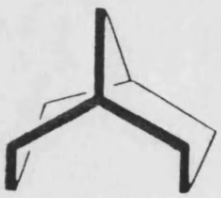
2.1 Conformation

Bicyclo[3.3.1]nonane itself may exist in any of the following three conformations: double(or twin)-chair (cc), chair-boat (cb) and double-boat (bb). All these are subject to some destabilising interactions of non-bonded atoms. It has been shown that the double-chair conformation is the most stable by approximately $10.5 kJmol^{-1}$/mole.[101]

boat, boat (bb)

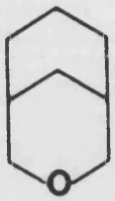


chair, boat (cb)

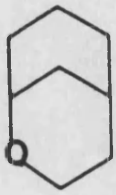


chair, chair (cc)

In oxoanalogues of the type (68) the double-chair conformation is destabilised relative to the boat-chair conformation, however they were still shown experimentally to be double chairs.[102]



(68)



(69)

With the use of molecular mechanics it has been computed that introduction of an oxygen in the 2-position causes a destabilization of the c-c with respect to the b-c conformation.[103] In 2-oxabicyclo [3.3.1]nonane (69) the c-c and the b-c are computed to be about equally strained.[103]

2.2 Synthesis

(2)-3-oxabicyclo [3.3.1]nonanes are a class of compounds that have been synthesised mainly for conformational or spectroscopic studies. Conversely they have also been synthesised in conjunction with other ring systems to give highly functionalised derivatives. None of the compounds required in this project are known. Syntheses of bicyclo[3.3.1]nonanes previously described in the literature have come in five types inherent to

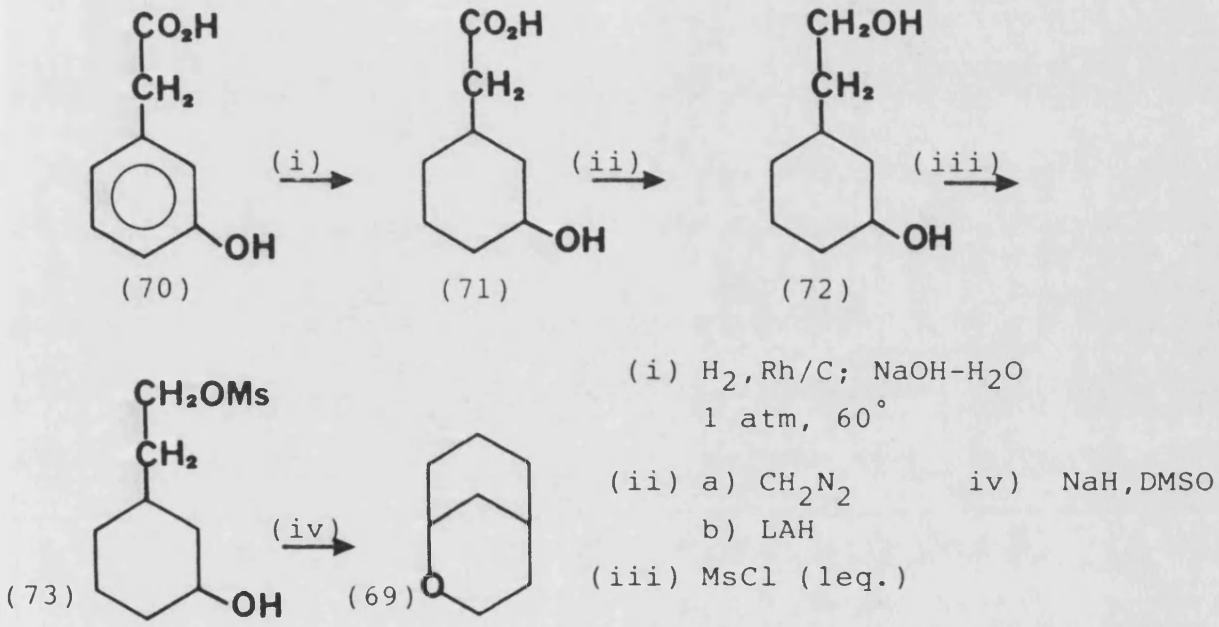
the basic ring structure: 1) annulation of cyclohexane derivatives; 2) annulation of cyclooctane derivatives; 3) ring cleavage of adamantane derivatives; 4) skeletal isomerization reactions and 5) syntheses starting from other bicyclo[3.3.1]nonanes. The majority of (2)-3-oxabicyclo[3.3.1]nonanes have been synthesised either via cyclohexane derivatives or from other (2)-3-oxabicyclo[3.3.1]nonanes.

2.2.1 Syntheses of 2-oxabicyclo[3.3.1]nonanes

This series is known, although most of the compounds are poly-substituted or are in the form of a lactone (i.e. 2-oxabicyclo[3.3.1]nonan-3-one). Syntheses in this area have concentrated on two types of approach: 1) cyclisation of a suitably substituted cyclohexane and 2) iodolactionization of a suitably substituted cyclohexene.

Using the first approach 2-oxabicyclo[3.3.1]nonane (69) has been synthesised.[104] Starting from 3-hydroxyphenyl acetic acid (70) which was hydrogenated in an alkaline medium with Rh/C as a catalyst to give a cis/trans mixture of the corresponding cyclohexane derivative (71). After esterification with diazomethane and reduction with LAH a cis/trans mixture of 3-hydroxycyclohexyl-ethanol (72) was obtained. Reaction with 1 equivalent of methane-sulphonylchloride afforded the monomesylate (73) which was cyclised in an extremely low yield (4%) to 2-oxabicyclo[3.3.1]nonane (69) with the use of NaH in DMSO. (Scheme 15) The very low yield can be attributed to two factors: 1) only the cis isomer can react and

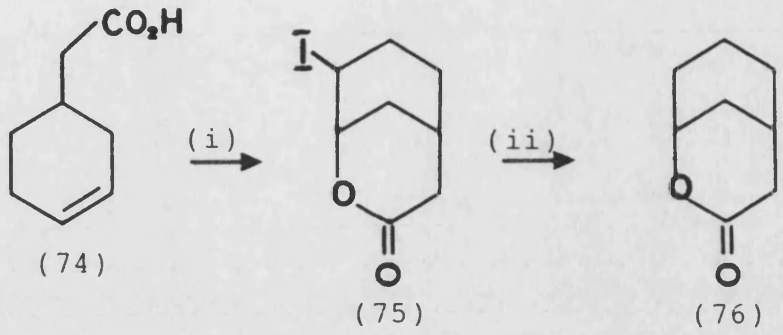
2) the preferred diequatorial conformation of the substrate.



Scheme 15

2-oxabicyclo[3.3.1]nonan-3-one (76) has been synthesised by the second type of approach through iodolactionization[105] of 3-cyclohexene-1-acetic acid (74) followed by reductive removal of iodine from the iodolactone (75)[105] with tributylstannane.[106] (Scheme 16)

This synthetic method has been used for a wide variety of derivatives of 2-oxabicyclo[3.3.1] nonanes.[107,108]



(74) (75) (76)

(i) KI/I_2

(ii) Bu_3SnH

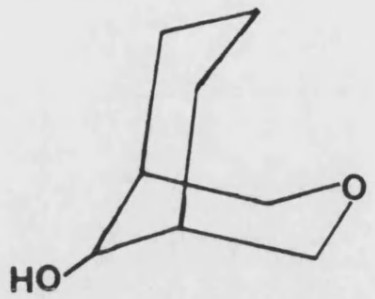
Scheme 16

2.2.2. Syntheses of 3-oxabicyclo[3.3.1]nonanes

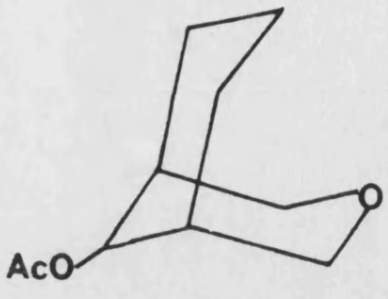
There have been three main approaches to the syntheses of 3-oxabicyclo[3.3.1]nonanes: 1) Reactions of cyclohexene using Prins type reactions; 2) Cyclisation of suitably substituted 1,3 cyclohexane derivatives and, 3) from the pyrrolidine enamine of tetrahydro(4H)pyran-4-one.

A number of 3-oxabicyclo[3.3.1]nonanes have been isolated as minor products from the mineral acid-catalyzed reaction (Prins reaction) of cyclohexene with formaldehyde in acetic acid as solvent.[109] Compounds (77) and (78) were isolated as minor products from the reaction mixture.

Other derivatives have been synthesised via this type of approach. When 1-phenylcyclohexene was subjected

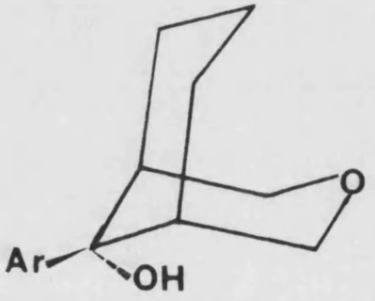


(77)

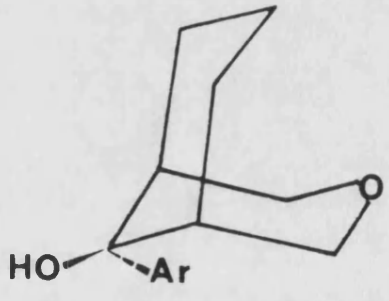


(78)

to the Prins reaction, two diastereoisomeric products (79) and (80) were obtained.[110,111]



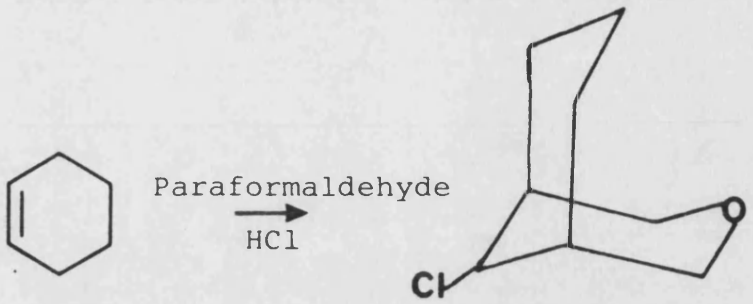
(79)



(80)

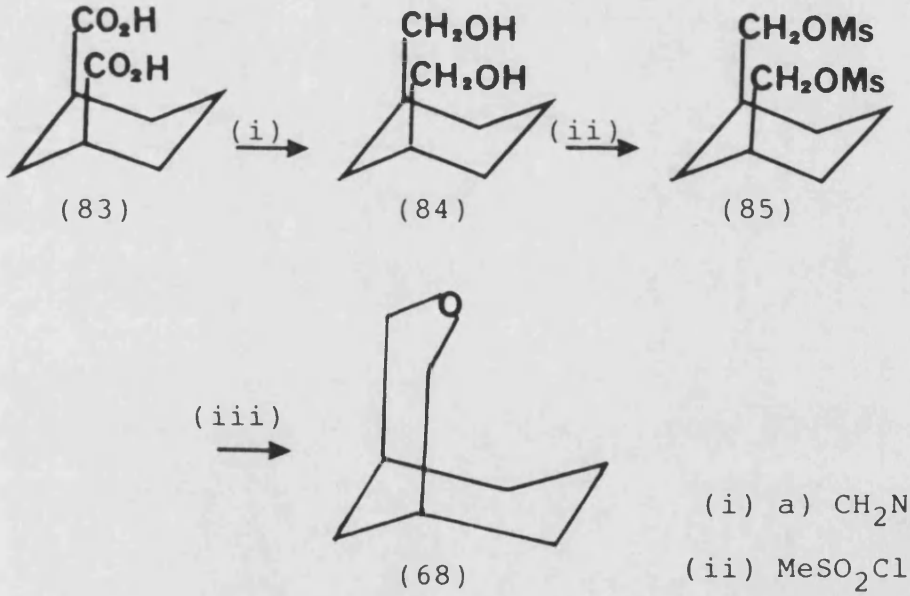
Many Russian workers have developed similar schemes and have obtained complementary results.[112,113] One group of workers used HCl and obtained 9-chloro-3-oxabicyclo[3.3.1]nonane (82).[112]

Various derivatives have been obtained using the procedure of Haggis and Owen.[114] Cyclohexane cis-1,3-dicarboxylic acid (83) was converted to the methanol derivative (84). Reaction with methanesulphonyl chloride



(81) (82)

afforded the mesylates (85) which gave the desired 3-oxabicyclo[3.3.1]nonane (68) on the reaction with aqueous KOH. (Scheme 17).



(83) (84) (85) (68)

(i) a) CH_2N_2 b) LAH

(ii) $MeSO_2Cl$

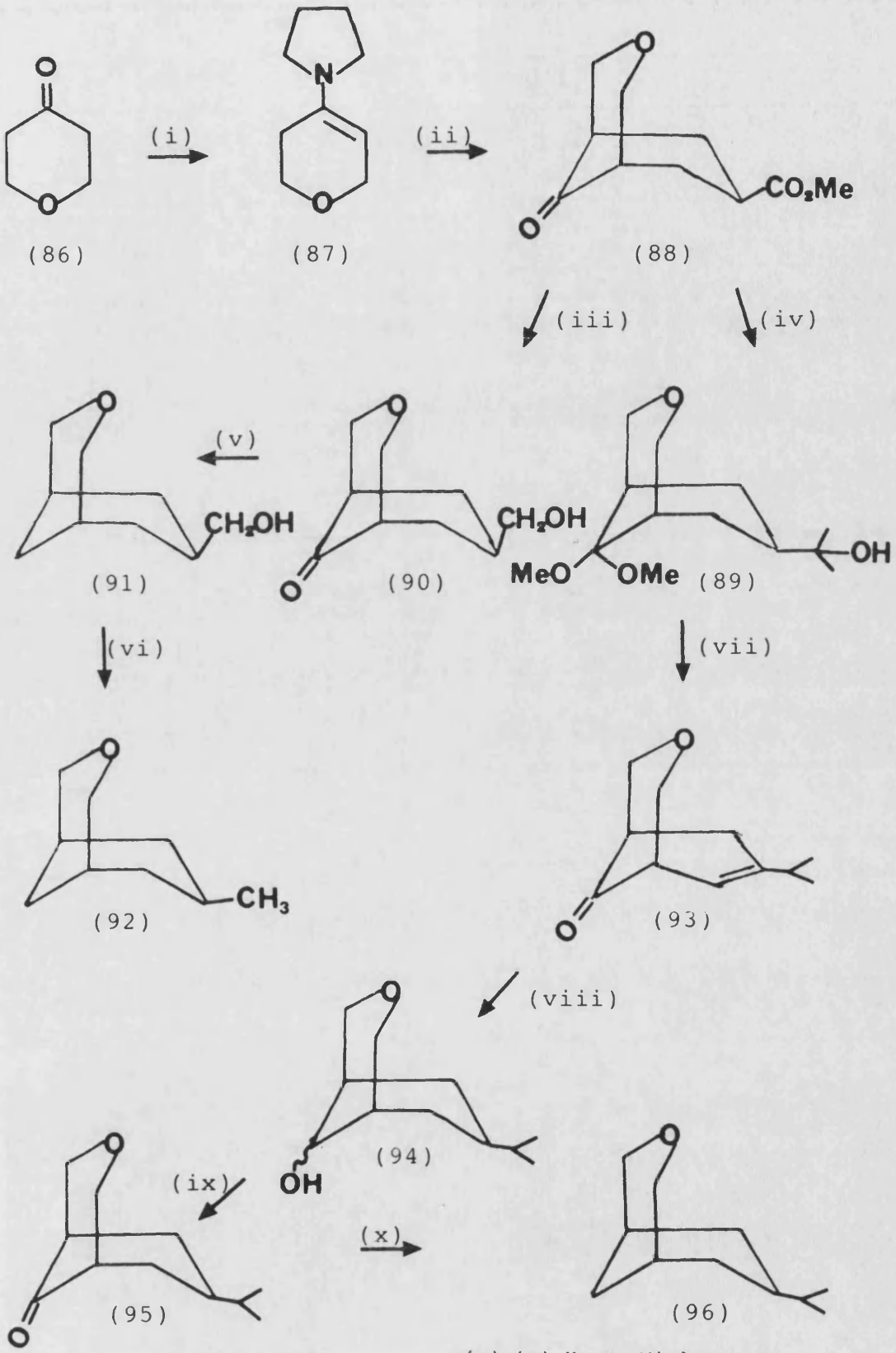
(iii) KOH

Scheme 17

One group cyclised the dimethanol compound (84) direct by distillation from alumina[115] to obtain the desired compound in 15% yield.

Cyclisation of suitable 1,3 cyclohexane derivatives has proved very popular,[116,117] although the method of cyclisation prevents the use of epimerisable groups as complex mixtures are obtained with the use of KOH. To overcome this problem Peters et al[116] developed an alternative approach when they were synthesising 7-alkyl-3-oxabicyclo[3.3.1]nonane for mass spectroscopic studies. 7-endo-methyl- and 7-endoisopropyl-3-oxabicyclo[3.3.1] nonanes (92,96) were synthesised starting from tetrahydro (4H)pyran-4-one (86). α,α'-Annelation of the pyrrolidine enamine (87) with methyl β,β'dibromoisobutyrate afforded methyl 3-oxa-9-oxobicyclo[3.3.1]nonane-7-endo carboxylate (88). After protection of the 9-oxo function as the dimethyl acetal, reduction with LAH and acid hydrolysis gave the 7-endo-methanol compound (90). The 9-oxo-function was removed by a Huang-Minlon reduction (91). Tosylation of the resulting methanol compound and subsequent reduction with LAH gave 7-endo-methyl-3-oxobicyclo[3.3.1] nonane (92). Reaction of (88) with MeMgBr resulted in the corresponding dimethyl-carbinol (89). Treatment with 4N H_2SO_4-dioxane (1:1) caused hydrolysis of the acetal and dehydration to yield 7-isopropyl-9-oxo-3-oxabicyclo[3.3.1]non-6-ene (93). This was hydrogenated selectively to give 9-hydroxy-7-endo-isopropyl-3-oxabicyclo[3.3.1]nonane (94). After oxidation of the

Scheme 18



(i) Pyrrolidine

(ii) a) $(BrCH_2)_2CHCO_2Me$
b) H^+

(iii) a) LAH
b) H^+

(iv) a) MeMgBr
b) H^+

(v),(x) Huang-Minlon

(vi) a) TsCl
b) LAH

(vii) H^+-H_2O

(viii) H_2;Pd/C

(ix) CrO_3

9-hydroxy function (95), a Huang-Minlon reduction afforded the desired 7-endo-isopropyl-3-oxabicyclo[3.3.1] nonane (96). (Scheme 18)

Most of the synthetic routes to (2)-3-oxabicyclo [3.3.1]nonanes have been developed for conformation or spectroscopic studies and so consequently yield has not been too important and in most cases (2)-3-oxabicyclo [3.3.1]nonanes have been obtained in painfully low yields. One of the aims of this project was to develop high yielding synthetic routes to 2-3-oxabicyclo[3.3.1]nonanes, so that they could consequently be used as viable synthetic intermediates.

RESULTS AND DISCUSSION

3. Approaches to the synthesis of 2-oxabicyclo[3.3.1] nonanes

3.1 Synthetic strategy

Many of the approaches to the synthesis of 2-oxabicyclo[3.3.1]nonanes involve the cyclisation of a suitably 1,3 disubstituted cyclohexane. The problem associated with this is that the groups involved in the formation of the final ring must be axial on the cyclohexane ring already present (Figure 1).

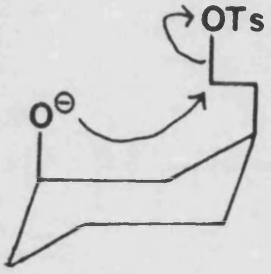
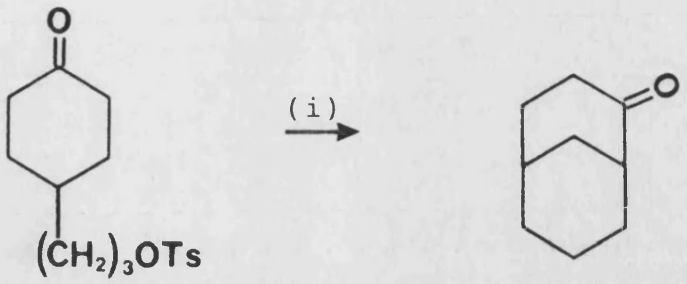


Figure 1

A route was required that did not involve this method of ring formation. Obviously, it is energetically more costly to bring two groups to a 1,3-diaxial orientation than to get a single group into an axial position. Therefore we envisaged using an internal enolate alkylation process, where only the alkylating group has to be in an axial orientation. We attempted to use a cyclisation analogous to that of Marvell et al[120] in their synthesis of bicyclo[3.3.1]nonan-2-one (98).

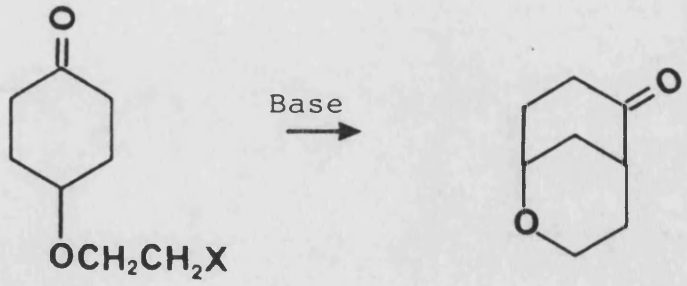


(97) (98)

Reagent: (i) tBuOK,THF,40°

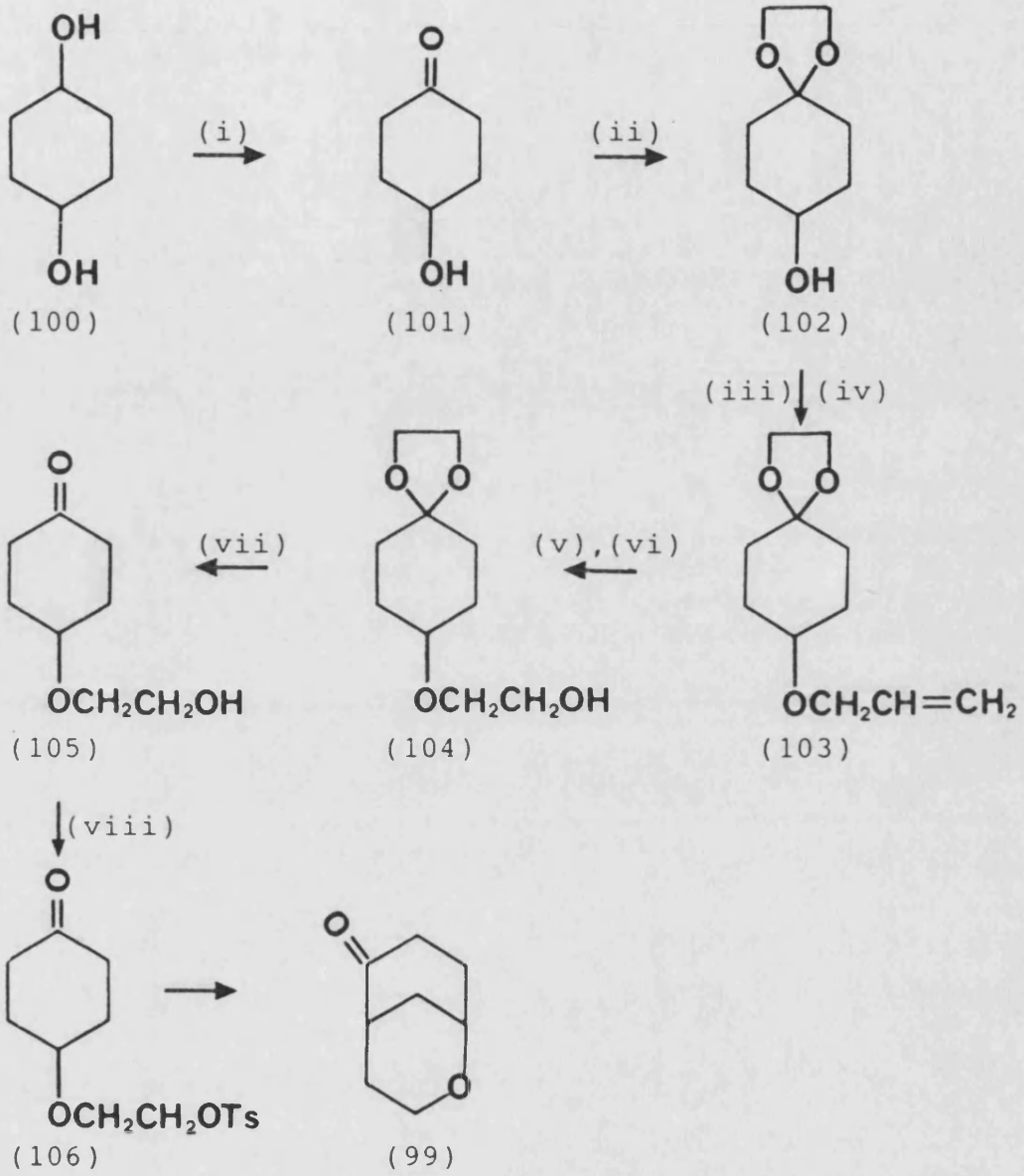
Scheme 19

In our case, we used an oxo-analogue of a 4-substituted cyclohexanone. In this approach it was envisaged that 4-ethoxy substituted cyclohexanones would afford the target system.



x = leaving group (99)

Scheme 20



Reagents:
(i) Jones oxidation
(ii) Ethylene glycol, benzene
(iii) NaH
(iv) Allyl bromide, KI, DMF
(v) O_3
(vi) $NaBH_4$
(vii) H^+/H_2O
(viii) TsCl, Pyridine

Scheme 21

3.2 Synthesis of 4-ethoxy substituted cyclohexanones

It was visualised that the 4-ethoxy substituted cyclohexanones would be synthesised from 4-hydroxy cyclohexanone (101) (Scheme 21).

This latter compound is not very stable thermally, and is not available commercially. The method chosen was that of Haslanger and Lawton,[121] which involved the partial oxidation of cyclohexane-1,4-diol (100) using 0.95 equivalent of Jones reagent to yield 4-hydroxy cyclohexanone (101) as a pale green oil. Haslanger and Lawton used this without purification. However, unpurified 4-hydroxycyclohexanone (101) decomposed significantly, even overnight, particularly in the presence of oxygen. This occurs by dehydration, which is effected by residual acid from the Jones reagent. Consequently, it was purified by dry-column "flash" chromatography and gave a 54% yield of a colourless oil. Once purified it could be stored indefinitely. The ethylene ketal of 4-hydroxycyclohexanone (102) was prepared using crude alcohol by the method of Haslanger and Lawton[121] and was obtained in 57% yield. The 8-(2-propenyloxy)-1,4 dioxaspiro[4.5]decane (103) was prepared by the reaction of the sodium alkoxide of 8-hydroxy 1,4 dioxaspiro[4.5]decane with allyl bromide in DMF; better yields are obtained (~10%) if 20% w/v of dry potassium iodide is present in the reaction mixture. This is probably due to a Finkelstein type reaction, i.e. halide exchange. The yield was approximately 70%.

The i.r. spectrum gave the characteristic double bond stretch at $1640cm^{-1}$. The ^{1}Hnmr spectrum showed the typical peaks for the allyl group, a complex multiplet at δ6.16-5.74 ($CH=CH_2$) and a triplet at δ5.4-5.04 ($CH=CH_2$). The evidence for the ether linkage is seen at δ4.01. The ^{13}Cnmr was in accord with the desired compound. Also, using chemical ionization a molecular ion was seen in the mass spectrum at m/e 199(M^{+1}). The allyl ether (103) was subjected to ozonylsis with a reductive work up using sodium borohydride.[122] Sodium borohydride was chosen as this decomposes the ozonide to give an alcohol, which was synthetically more useful in our case than the usual aldehyde. This reaction worked very well and gave yields of over 90% of 8-(2-hydroxyethoxy)-1,4 dioxaspiro[4.5]decane (104), which t.l.c. (PE/EA,5:1) and ^{1}Hnmr indicated was pure enough to use without any purification. This was submitted to an acidic hydrolysis using either acetic acid/H_2O or perchloric acid with both methods giving comparable yields of ~70% of 4-(2-hydroxyethoxy)cyclohexanone (105), which were purified by vacuum distillation. Spectral data were in accord with the desired compound. The i.r. spectrum showing alcohol ($3455cm^{-1}$) and ketone ($1710cm^{-1}$) peaks. The alcohol (105) was converted to the tosylate (~90% yield), which showed no hydroxyl group in the infra red spectrum and was used without purification.

3.3 Cyclisation attempts

3.3.1 With tosylate as leaving group

Cyclisation was attempted using the tosylate as a leaving group via an internal enolate alkylation process as mentioned before. A number of base/solvent systems were tried and these are summarised in Table 1.

	Base	Solvent
1.	LDA	THF
2.	KO^tBu	THF
3.	KO^tBu	^tBuOH
4.	NaH	DME

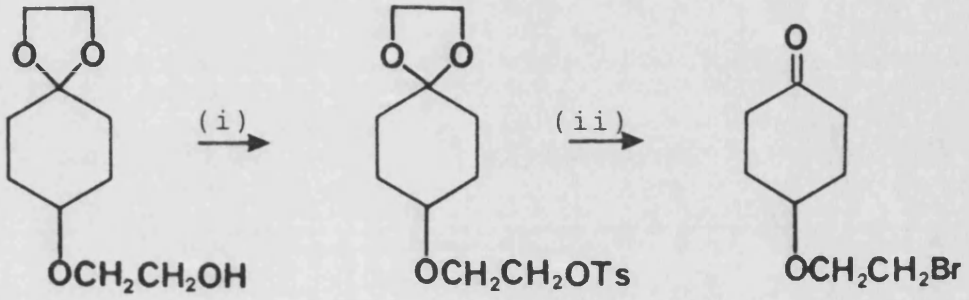
Table 1

The LDA/THF reaction with 4-(2-tosyloxyethoxy) cyclohexanone (106) yielded mainly unreacted starting material. The KO^tBu/THF and NaH/DME procedures yielded unidentifiable mixtures containing starting material. KO^tBu/THF reaction yielded 4-(2-hydroxyethoxy)cyclohexanone (105) the hydrolysis product of the tosylate. Cyclisation attempts with tosylate as a leaving group had proved to be unpromising. Consequently an alternative leaving group was sought.

3.3.2 Bromide as leaving group

The modification chosen was to use bromide as the leaving group. This was achieved by modifying the

synthetic route slightly by utilizing the method of Becker.[123] This involved the formation of the tosylate of 8-(2-hydroxyethoxy)-1,4 dioxaspiro[4.5]decane (104), which was refluxed in acetone with lithium bromide. This was convenient because replacement of the oxytosyl group by the bromo function and deprotection of the carbonyl were achieved in one step. The product was purified by vacuum distillation in 66% yield.



(104) (107) (108)

Reagents: (i) TsCl,Py,O° (ii) LiBr, Acetone, reflux

Scheme 22

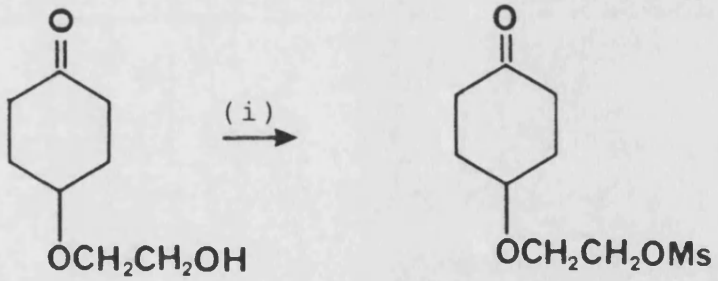
Cyclisation attempts were carried out on the bromo compound. Two base/solvent systems were tried: 1) LDA/THF and 2) KO^{t}Bu/benzene. The LDA reaction gave only unreacted starting material. The KO^{t}Bu/benzene gave no identifiable product.

A hypothesis concerning the difficulty encountered in cyclisation was whether we had chosen the appropriate leaving group and therefore it was decided to change the leaving group. This idea was supported by observations

made by Schultz and Dittami.[124] They found that cyclisation yields were dramatically changed depending on the choice of leaving group, in their case going from chloride to iodide. Therefore it was decided to prepare the mesylate as the leaving group as this would be more reactive than the previous leaving groups.

3.3.3 Mesylate as leaving group

4-(2-hydroxyethoxy)cyclohexanone (105) was mesylated at room temperature, although the aqueous work-up was effected rapidly and at ice-bath temperature to avoid undue decomposition of the product. The mesylate was readily purified by "flash" chromatography.



(105) (109)

Reagents: (i) MsCl, DMAP, Py, RT

Scheme 23

Two base/solvent systems were tried: 1) LDA/THF; 2) KO^{t}Bu/Benzene. However, the results were as before; there was no evidence to suggest that cyclisation had occurred, although absence of the mesylate was shown.

This seemed to contradict the hypothesis that an unreactive leaving group was the cause of failure to cyclise, since such a description is hardly applicable to the oxymesyl group.

3.4 Rationale on failure of cyclisation attempts involving 4-ethoxy substituted cyclohexanones

It was difficult to account for the curious difficulty encountered in achieving this cyclisation. To recapitulate, one fact is known for certain; the situation has to be due to an effect of the ethoxy oxygen. This may be stated because: it is that function which represents the only difference between the failure of the cyclisation encountered in this project and success of analogous carbon chain reactions.[120,124]

There should be no problem in the formation of the enolate anion, the problem lies in why the resultant anion fails to undergo cyclisation by SN_2 attack.

The first idea to be considered was that the conformation required to enable cyclisation to occur was in some way sterically or energetically unfavourable. In considering the resonance stabilised enolate anion, figure (2) it was appreciated that effective overlap of p-orbitals throughout its π-system demands a more than usually rigid geometry of the carbonyl carbon, C(1). This is enforced by the shortening of the bond between C(1) and the Sp^2 hybridised C(2), which also adopts a trigonal disposition. The result is appreciable flattening of the usual chair conformation of the ring,

in a manner similar to that of cyclohexene.

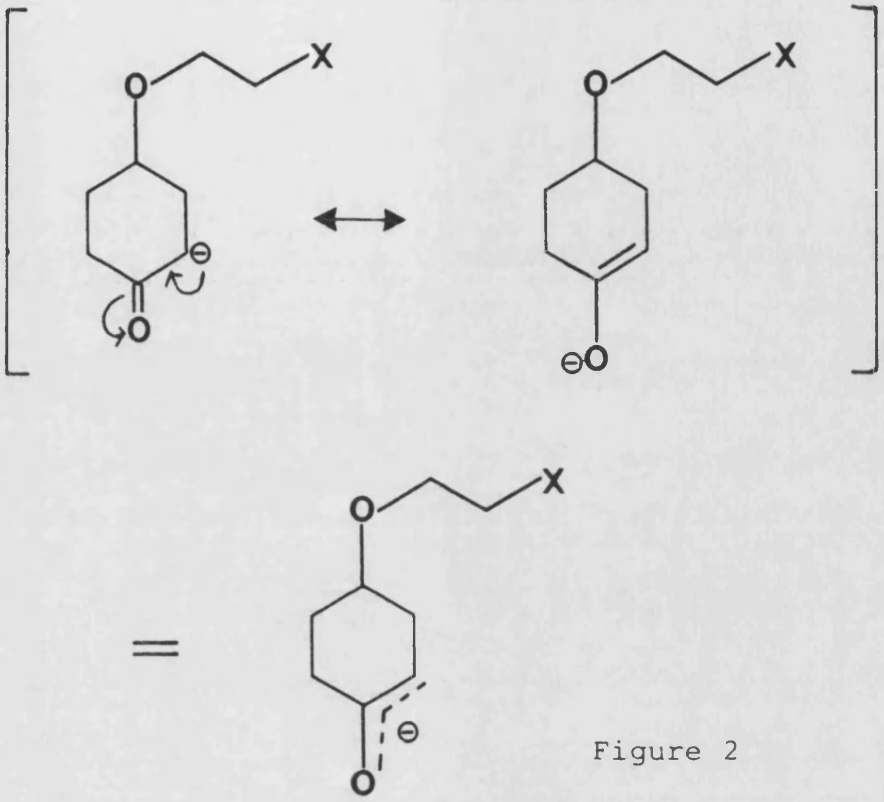
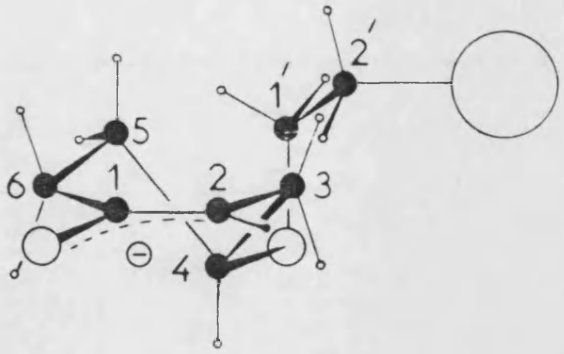


Figure 2

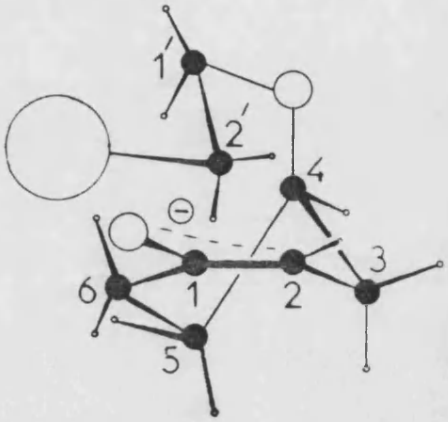
It would be anticipated that the most stable conformation would be the half-chair ring conformation in which the 4-substituent is equatorial (figure 3). In this conformation there is no way that C(2') can get close enough to C(2) to undergo attack by the enolate anion.

As mentioned earlier, to enable cyclisation to occur, the 4-substituent must be axial to the ring (figure 1).

Therefore consideration of purely steric effects does not help to explain why cyclisation has not occurred. It is true that the conformation in figure 3(b) is unfavourable compared to that of figure 3(a). However, equilibrium amounts of the former would be expected.



(a) half-chair, 4-ethoxy group eq



(b) half-chair, 4-ethoxy group ax

Figure 3

Were these then to cyclise, the conformation equilibrium would be disturbed in favour of figure 3(b). Such a process would continue until cyclisation was complete. This is underlined by the fact that the analogous cyclisation, where the ethoxy oxygen is replaced by CH_2, does occur. This cannot be explained by purely steric considerations. The magnitude of the unfavourable interaction between H(6β) and CH_2 would be anticipated as greater, and not less, than between H(6β) and O.

The implication of this evidence is that there is, in the oxygen ring formation, an electronic effect which disfavours cyclisation. This would obviously not manifest itself in the analogous carbon chain cyclisation. It seems likely that straightforward

repulsion between the ethoxy oxygen and the enolate anion can also be discounted.

In order to suggest a reason why cyclisation did not occur, the process of nucleophilic attack is reviewed. It has long been known that SN_1 processes are considerably assisted by the presence of an electronegative group α- to the leaving group, the so-called "α-effect".[6] (figure 4)

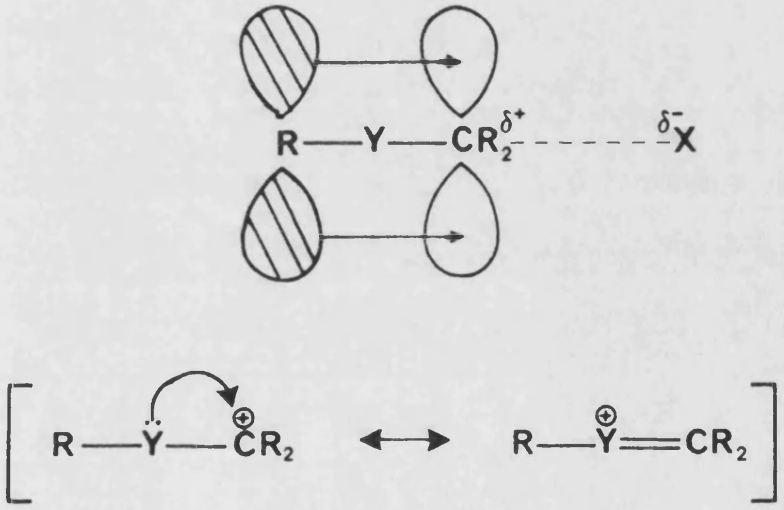


Figure 4

As shown in figure 4, this has been ascribed to a delocalisation of electron density from a filled orbital on Y towards the CR_2 group. The result is a stabilisation of the developing positive charge on CR_2. By this means, the expulsion of the leaving group X is facilitated. Alternatively, the effect can be regarded as classical resonance stabilisation of a carbonium ion by the adjacent Y group, as shown in figure 4.

Now we go on to consider the consequences of moving the Y group one carbon atom further away from CR_2.

There are two ways of regarding this as shown in figure 5. In figure 5(a), Y is considered to occupy a position β to CR_2, where effective overlap of filled orbital on Y with one on CR_2 is not possible. Figure 5(b) shows Y as a substituent of the α-carbon, which is capable of a type of internal SN_2 attack which helps to expel X. This is known as "anchimeric assistance". In the former case, the influence that is beneficial to nucleophilic substitution, the +R resonance stabilisation is not possible. However, the destabilising inductive influence may now become significant, assuming it can be exerted through two bonds. Evidence that OR groups have a significant inductive effect comes from the fact that 2-alkoxyethyl halides undergo solvolysis much more slowly than ethyl halides.[125] Gould commented,[126] "Therefore

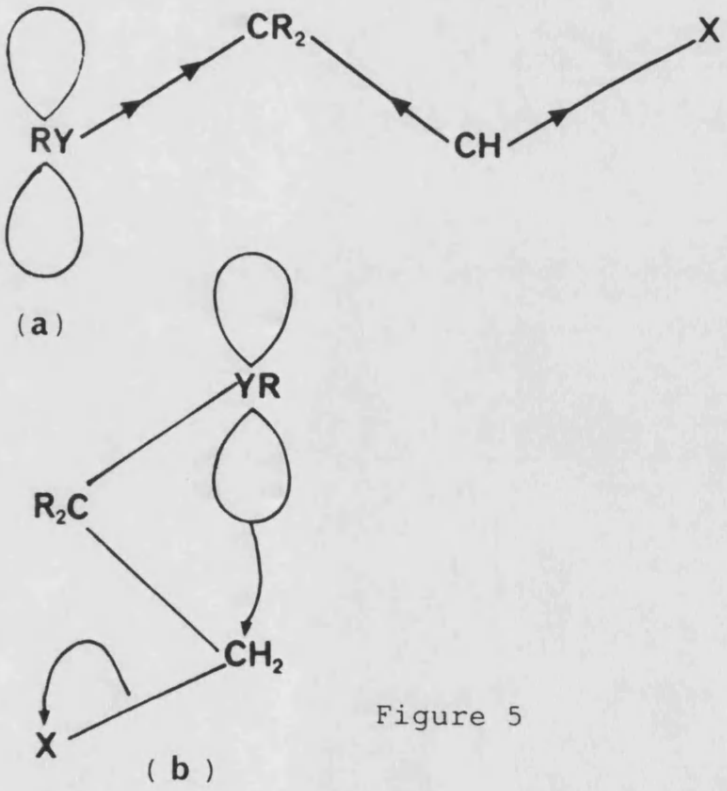


Figure 5

such substituents, except for cases involving neighbouring group participation will retard unimolecular substitutions."

It must next be considered how these factors would influence bimolecular substitution. Initially one would think that an electron-withdrawing group as Y, by increasing the magnitude of $\delta+$ on CR_2, would assist SN_2 attack. However, there is no sharp dividing line between SN_1 and SN_2 reaction mechanisms. These two cases are in effect, the extremes of a wide spectrum.

Now, considering the SN_2-type transition state, it is convenient to consider the two opposing situations (figure 6). The first case (a), where Z is a negatively charged, powerful nucleophile such as OH^-. Here n=1, the transition state is negatively charged, the initial product is neutral. In the transition state, Z supplies electron density to the centre under attack faster than X can extract it; this leads to the development of $\delta-$ at C. Any electron-withdrawing Y group will certainly assist the reaction.

However, for case (b) where Z is a neutral nucleophile, supplying only a lone pair, for example H_2O, the situation is different.

Where n=O, the transition state will progressively develop a positive charge at the carbon centre being attacked, and the initial product carries a full positive charge. In the transition state, X will withdraw electron density faster from the attacked centre than can be supplied by Z. Consequently a $\delta+$ charge forms at this

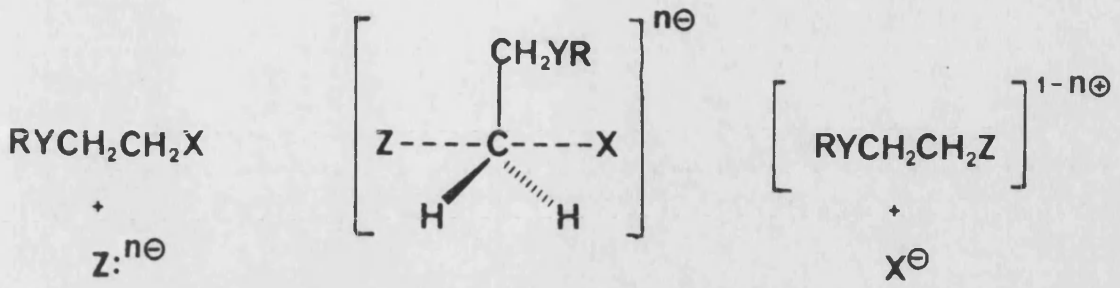


Figure 6

centre. Clearly, any electron withdrawal will merely exacerbate this situation and will retard the reaction in this case.

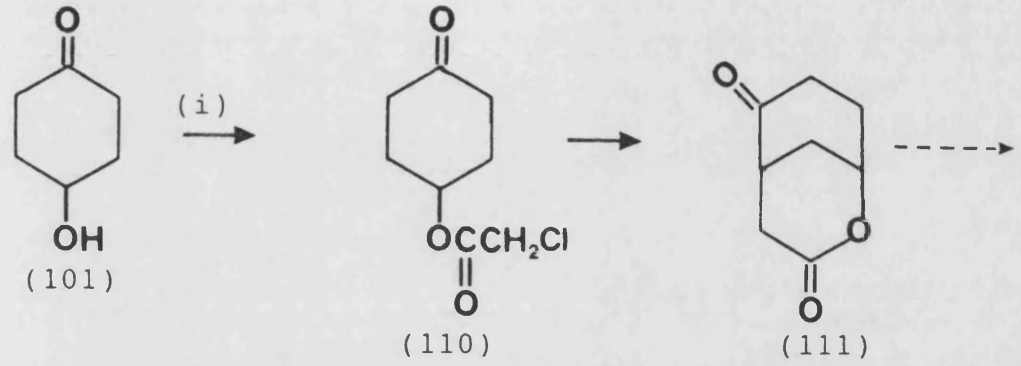
The question which one has to ask now is which case does nucleophilic attack by the enolate anion in these cyclisation attempts resemble? The answer to this will indicate whether or not the ethoxy oxygen can be expected to assist or retard cyclisation. Superficially it would appear to resemble case (a). However, although the enolate is an anion, the electron is delocalised over three atoms (see figure 2). Therefore, the rate of donation of electron density by the anion, to the transition centre, will depend upon the magnitude of its resonance stabilisation. This will oppose such a donation of electron density. A consequence of the leaving group extracting its electron pair from

the C(2') centre faster than the rate of donation of electron density by the attacking enolate would be a build up of positive charge at that atom. In such a circumstance it is appreciated that any inductive effect of a β-oxygen atom would retard the reaction, possibly prohibitively. Furthermore, another look at figure 3(b) will indicate that the conformation required for cyclisation is closer to that depicted in figure 5(a) than in figure 5(b). That is anchimeric assistance by alkoxy oxygen during the reaction, in order to stabilise that positive centre is effectively ruled out. Consequently it is believed that failure of these cyclisations is due to a β-oxygen effect caused by an inductive effect of the ether oxygen.

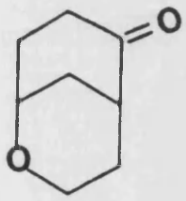
3.5 Cyclisation attempts using 4-chloroacetyl cyclohexanone (110)

The internal alkylation process using 4-ethoxy substituted cyclohexanones seemed to suffer from a oxygen effect which proved prohibitive to the reaction. It was decided to make use of the α-effect. That is to attempt cyclisation on a 4-ethoxy substituted cyclohexanone, substituted suitably α to the leaving group with some function capable of donating electron density to the SN_2 transition state. This would lead to stabilisation of the transition state, by reversing the inductive effect of the ethoxy oxygen because of the resonance effect of the α-substituent.

It was hoped that with a suitable α-substituent, there should be no reason to prevent the occurrence of cyclisation. It was this idea that gave rise to the second approach.



(101) (110) (111)



(99)

Reagents: (i) $ClCCH_2Cl$, Py, Et_2O

Scheme 24

There were three excellent reasons for the choice of a 4-oxychloroacetyl substituent on cyclohexanone. Firstly, it replaces the CH_2 α-to CH_2X by a carbonyl group. This has a π-system perfectly disposed to stabilise the SN_2 transition state as carbonyls are known to exhibit the α-effect.

Secondly it is easily and cheaply prepared in two steps from (100). For chloroacetylchloride, the much greater reactivity of the acetylchloromethyl function, compared to that substituted α-to the carbonyl, makes

alkoxide attack almost exclusive at the former position.

Thirdly, (110) has the additional property necessary to make this approach a feasible synthesis of (99). That is, when cyclised to 2-oxabicyclo[3.3.1]non-3,6-dione (111), the 3-carbonyl function ought to be selectively reducible due to the difference in reactivity of ketone and lactone. 4-hydroxycyclohexanone (101) was chloroacetylated using pyridine as a base.[127] The spectroscopic data were in accord with the required structure. ^{1}Hnmr shows a first order quintet at δ5.22 which integrates to 1 proton and is assigned H(4). The expected 2-proton singlet for CH_2Cl is also clear at δ4.10. The remaining protons, on the ring, form a multiplet at 1.9 to 2.76. ^{13}Cnmr were also as expected, indicating one signal for CH, two for quaternary carbons and three for CH_2; all at shifts in close accord with those predicted by correlation tables. The most informative peaks in the CI mass spectrum were 191/3(M^{+1}) and 157(M^{+2}-Cl).

A number of cyclisation attempts were carried out on 4-(chloroacetoxy)-cyclohexanone (110) and these are summarised in Table 2.

LDA/THF was tried as a base/solvent system, where t.l.c. indicated a complex mixture. No attempt was made at separation. Another base/solvent tried was $KOBu^t$/THF, where a seven-component mixture was obtained. Apart from starting material which was one of the components, three other compounds were tentatively

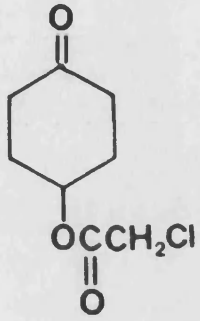
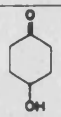
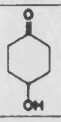
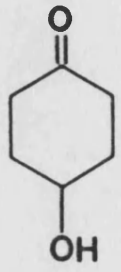
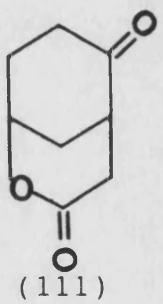
	REACTION CONDITIONS	RESULT
	LDA/THF, -78°C	complex mixture
	^{t}BuOk, THF, reflux	7 spots
	DBU, DCM, RT	
	Pyridine, reflux	
	NaH, DMF, RT	Baseline material

Table 2

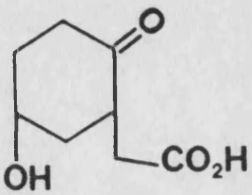
identified. The two other components were unidentifiable. The three compounds identities are believed to be: 4-hydroxycyclohexanone, which was identified by comparison of the spectral data with that of known material. One of the components was believed to be 2-oxabicyclo[3.3.1] non-3,6 dione (111). I.r. spectroscopy showed two



(101)



(111)



(112)

carbonyl stretches, one for the lactone ($1740cm^{-1}$) and one for the cyclic ketone ($1717cm^{-1}$). The ^{1}Hnmr showed a multiplet at δ5.15, which integrated to 1 proton and was assigned as the hydrogen attached to the bridgehead nearest the ether oxygen. The rest of the ring protons were found between δ2.6-1.8 as a complex multiplet, which integrates for nine protons. The fact that no 2-proton singlet for CH_2Cl is seen at δ4.10 indicates that this grouping is no longer present. In the mass spectrum the molecular ion was seen at m/e 154 also with a peak at m/e 109 indicating the loss of CO_2 from the molecular ion. The base peak was at m/e 97 and due to $C_6H_9O^+$,

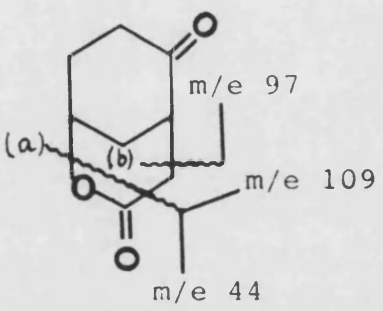


Figure 7

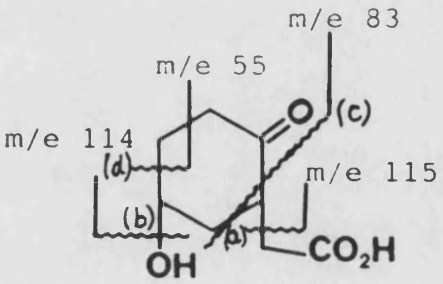
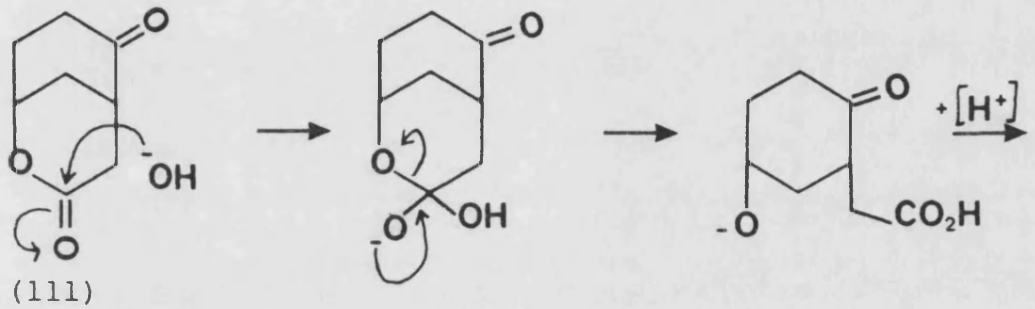


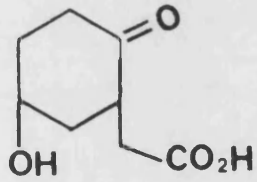
Figure 8

a common peak for cycloalkanones.

The other compound believed to be isolated was the ring opened form of (111), the opened lactone (112). This probably was the result of ring-opening as shown in figure 9.



(111)



(112)

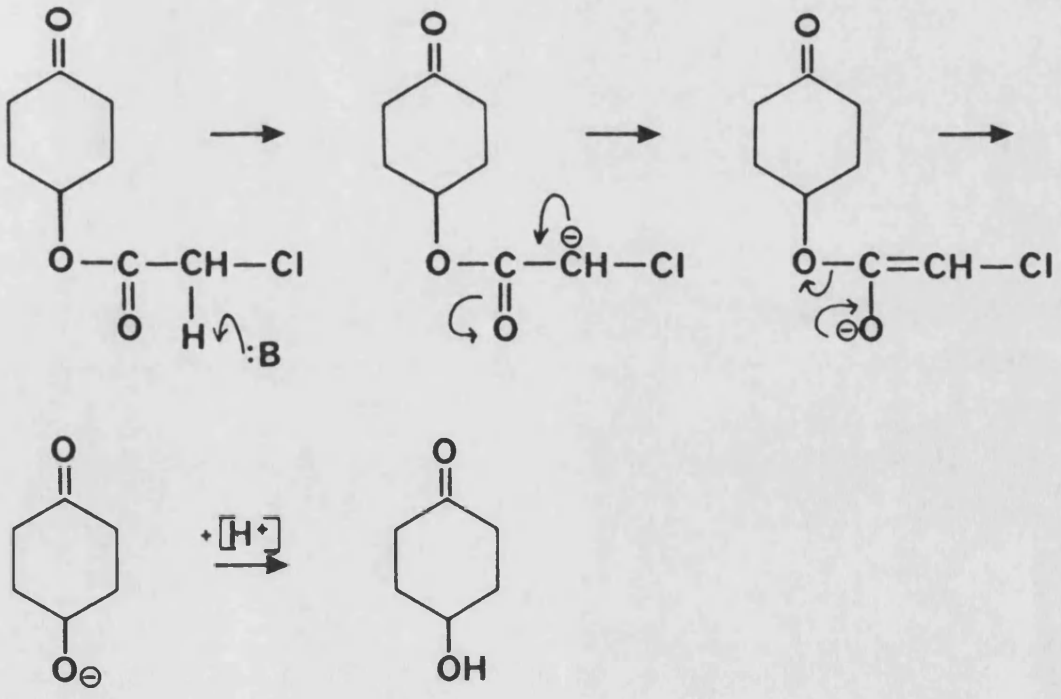
Figure 9 Mechanism for ring-opening of lactone (111)

The i.r. spectrum showing alcohol (3520), carboxylic acid (3150) and ketone (1710cm^{-1}) peaks. The ^{1}Hnmr spectrum showed a multiplet at δ5.1, which integrated for one hydrogen, a broad singlet at δ3.4 an hydroxy peak, which disappeared on D_2O exchange, a multiplet between δ2.6-1.8, which integrated for ten hydrogens. In the mass spectrum the molecular ion was seen at m/e 172, a peak at m/e 115, resulting from β-cleavage of the carboxylic acid and at m/e 97 due to $C_6H_9O^+$. The result of the mass spectra agreed with the usual

fragmentation patterns for a cyclohexanone.

Sodium hydride in DMF was used. However, these conditions completely decomposed the starting material and consequently no products were isolated. It was decided that conditions employed so far might be too harsh. Therefore we envisaged using a milder system. The two systems tried, refluxing in pyridine, and DBU in DCM, resulted only in the formation of 4-hydroxycyclohexanone (101). We imagined this as a result of EclB mechanism as shown in figure 10.

Figure 10 Formation of 4-hydroxycyclohexanone from 4(chloroacetyloxy)-cyclohexanone via an EclB mechanism



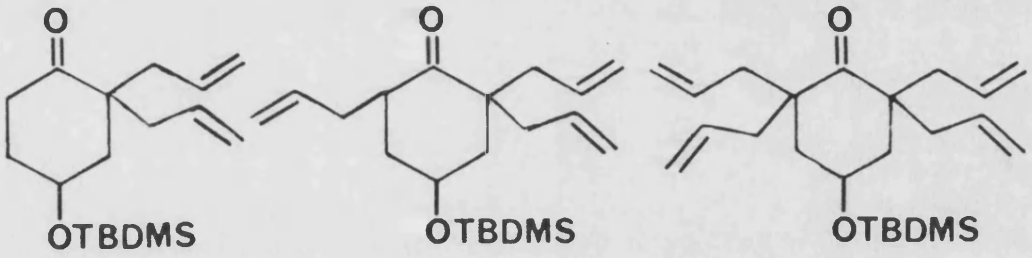
From our results it was becoming clear that a number of competing reactions were taking place. Also, a very important factor was the insignificant difference in acidity between the protons α to the carbonyl on the ring and those α to the carbonyl in the side chain. The indications were that those α to the carbonyl on the side chain were probably more acidic, which is not what we wanted. The idea behind the synthesis of the 2-oxabicyclo[3.3.1]nonanes was to use them as synthetic intermediates for more complex molecules, consequently a high yielding synthetic route was sought. It seemed unlikely that this approach would furnish such a route due to a number of competing reactions, which were not useful to us. Therefore it was decided to abandon this synthetic strategy.

3.6 Cyclisation via 2,4-disubstituted cyclohexanones

After our problems with the internal enolate alkylation approach it was decided to go back to the concept of cyclising a suitable 1,3 disubstituted cyclohexane even with all the inherent problems that this strategy imposed, which have been mentioned.

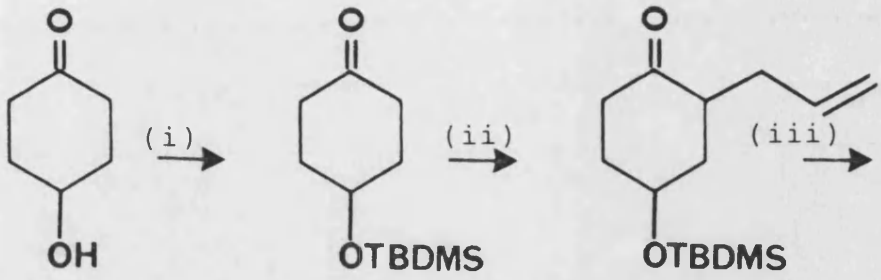
It was convenient to make use of a synthetic intermediate that we already possessed for this approach. We used 4-hydroxycyclohexanone (101), although in the protected form using t-butyldimethyl silyl as the protecting group (see scheme 25). This was prepared by the method of Wilcox and Grantham.[128] Attempts to alkylate this

with 2-t-butyldimethylsiloxyethylchloride failed, another example of the β-oxygen effect. Consequently alkylation was performed using allyl bromide. The desired compound was obtained as a mixture of cis and trans isomers approximately in a 1:1 ratio. Small amounts of the dialkylated (113), trialkylated (114) and tetraalkylated (115) products were obtained in approximately a 10% yield.

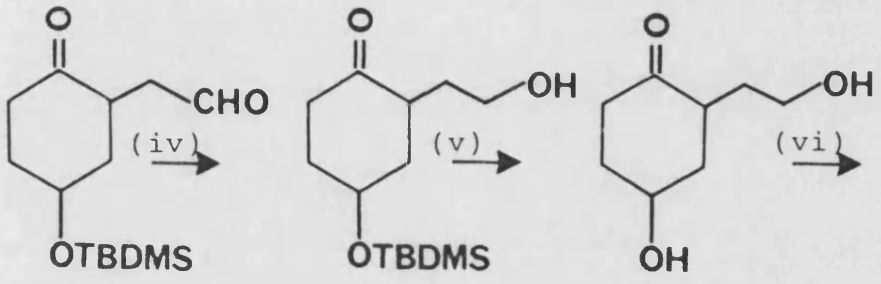


(113) (114) (115)

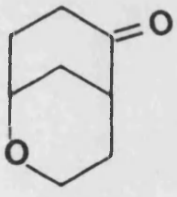
The required monoalkylated product (117) was obtained in a yield of 70%. No attempts were made to separate the isomers. Spectral data were in accord with the desired structure. I.r. spectrum gave a carbonyl (1711cm^{-1}) and a double bond (1639cm^{-1}) ^{1}Hnmr spectrum showed multiplets at δ5.65, 5.1 and 4.95 for the double bond part of the allyl group. A multiplet at δ4.15 for CHOTBDMS and a multiplet at δ2.9-1.7 for the rest of the protons apart from the protecting group which came as two singlets, one at δ0.95 for t-butyl and at δ0.15 for dimethyl. The ^{13}Cnmr showed the presence of two isomers as every peak in the spectrum was mirrored by another peak. The sizes of the peaks indicating



(101) (116) (117)



(118) (119) (120)



(99)

Reagents: (i) TBDMsCl, DMF, Imidazole
(ii) LDA, THF, HMPT, -78°, Allyl bromide
(iii) OsO_4, $NaIO_4$, Et_2O, H_2O
(iv) Formic acid, Et_3N, $RuCl_2(Pd_3)_3$
(v) Bu_4NF, THF

Scheme 25

the isomers in approximately a 1:1 ratio. In the cis and trans 4-t-butyldimethylsiloxy 2-(2'-propenyl)cyclohexanones, it would be expected that the OTBDMS group would prefer to be in an equatorial position due to its large steric requirement. Therefore the two most likely conformations for the cis and trans isomers are shown below with the OTBDMS group in an equatorial position in both cases.

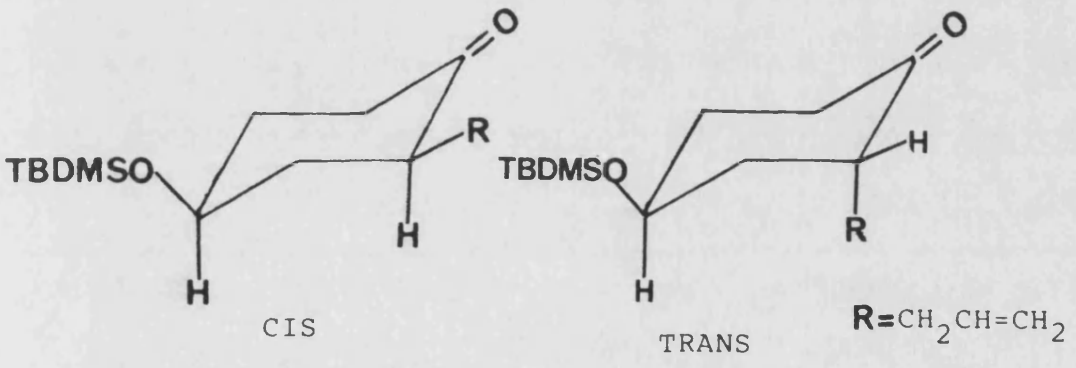


Figure 11

In the mass spectrum (C.I.) the molecular ion was seen at m/e 269 (M^{+1}). The next informative peak was at m/e 211 indicating the loss of t-butyl group. The base peak was at m/e 137 which is the result of the loss of the OTBDMS group.

The aldehyde (118) was prepared from the allyl compound (117)in a one pot process using osmium tetroxide/

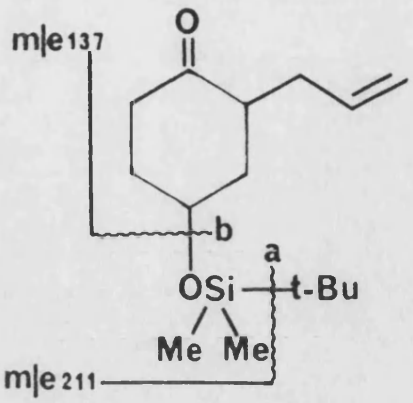


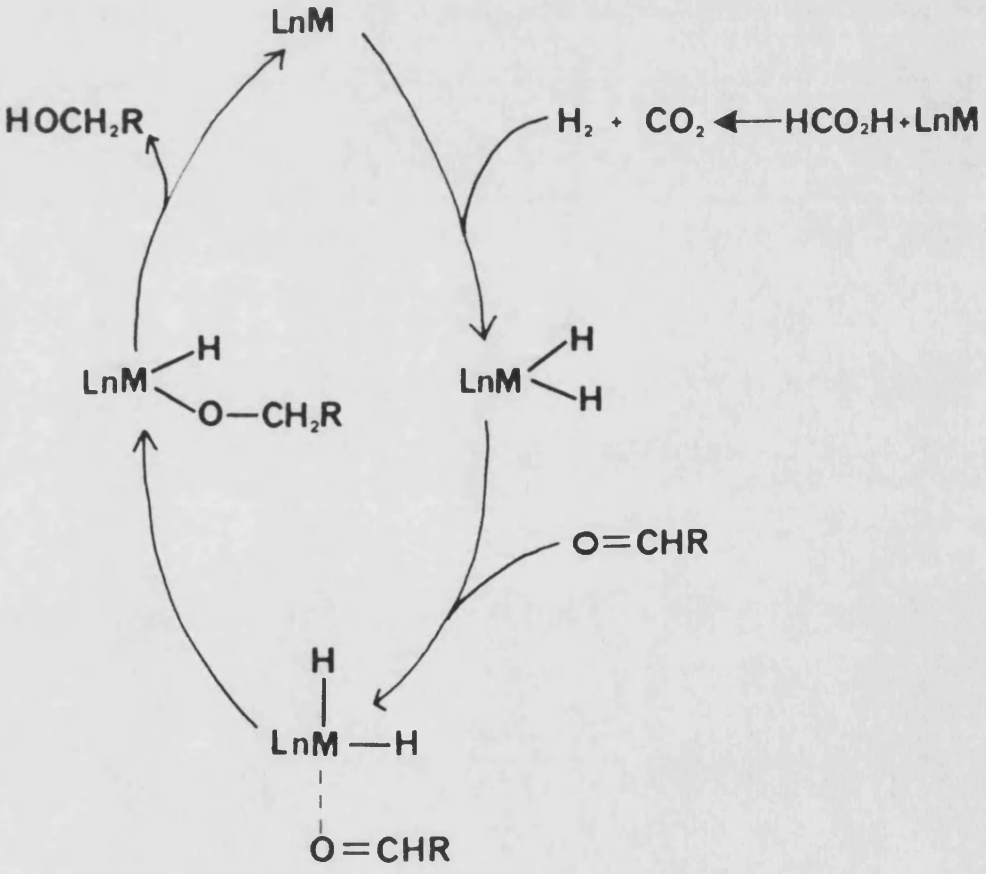
Figure 12

sodium metaperiodate in a two phase system of ether and H_2O[129] in a yield of 62%.

The ir spectrum showed two carbonyl stretches, one for ketone (1710cm^{-1}) and the other for the aldehyde (1695cm^{-1}). ^{1}Hnmr showed a multiplet for the aldehydic proton at δ9.8. The mass spectrum (C.I.) gave a molecular ion at m/e 271 (M^{+1}) and fragmentation of this was the same as the allyl compound (117) with loss of OTBDMS group giving the base peak at m/e 139.

The next step was the selective reduction of an aldehyde in the presence of a ketone. One equivalent of sodium borohydride was used but this gave some of the reduced ketone. The chosen method was that of Khai and Arcelli[130] who used the catalyst $RuCl_2(PPh_3)_3$ (0.4%) with triethylamine and formic acid. This gave the desired compound in a yield of 73%. The spectral data was in accord with the required structure. The mechanism of the reduction is not clear. The $RuCl_2(PPh_3)_3$ complex decomposes formic acid into hydrogen

and carbon dioxide. The hydrogenation of the aldehyde proceeds by the insertion of the carbonyl group into M-H that is generated by the oxidative addition of H_2. The alkoxo-hydrido complex thus formed reacts with the H_2 and reductively eliminates the product alcohol[131] (see scheme 26). There is believed to be competition between the aldehyde and ketone to coordinate to the catalyst and in all cases cited the aldehyde is reduced in preference to the ketone.[130]



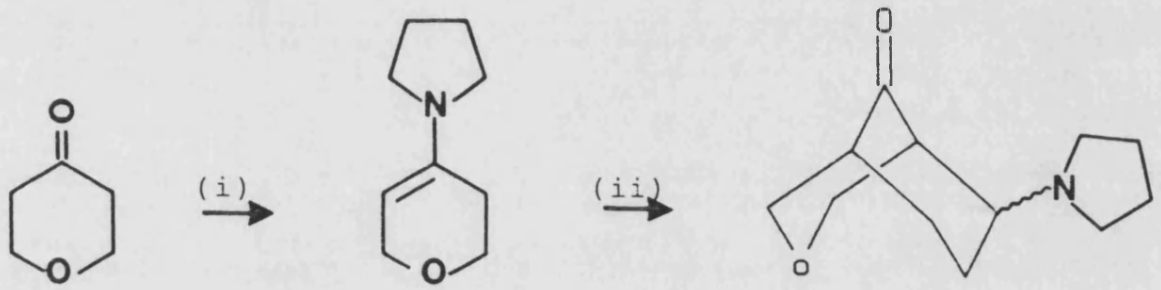
Scheme 26 Mechanism of hydrogenation

The silyl compound was deprotected using standard conditions,[132] to give the required dialcohol (120) in 54% yield for cyclisation. As mentioned before the compounds carried through this synthetic scheme are a mixture of cis and trans isomers and it is only the cis isomer that can obtain the 1,3-diaxial configuration required for cyclisation. So only 50% of the starting material would be expected to react. The method we tried for cyclisation was an "oxidative-reduction" dehydrative coupling using triphenylphosphine (TPP) and diethyl azodicarboxylate (DEAD).[133] Unfortunately none of the desired compound was obtained. It was at this point that we decided to abandon the attempted synthesis of 2-oxabicyclo[3.3.1]nonanes as more profitable work was being carried out in the other series, the 3-oxabicyclo[3.3.1]nonanes.

4. Synthesis of 3-oxabicyclo[3.3.1]nonanes

4.1 Synthetic strategy

It was envisaged obtaining the bicyclic system 3-oxabicyclo[3.3.1]nonane via the reaction of the enamine of tetrahydro-4H-pyran-4-one (122) with acrolein (Scheme 27).

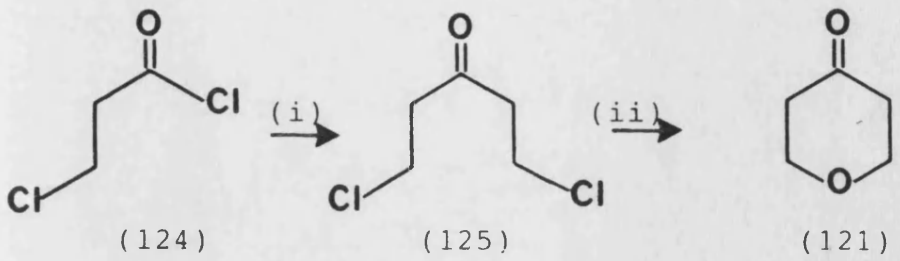


(121) (122) (123)

Reagents: (i) Pyrrolidine, benzene (ii) Acrolein

Scheme 27

Tetrahydro-4H-pyran-4-one (121) can be bought, but is expensive. Consequently a synthetic route was required. The method chosen was that of Owen and Reese,[134] and Arentzen, Yan Kui and Reese.[135] Tetrahydro-4H-pyran-4-one (121) can be obtained in a two step sequence from 3-chloropropionylchloride (124) (Scheme 28). The first step is the aluminium chloride-catalysed Friedel-Crafts acylation of ethylene with 3-chloropropionyl chloride (124) yielding 1,5-dichloro-pentan-3-one (125), which is then acid hydrolysed to give tetrahydro-4H-pyran-4-one(121) in 45% overall yield (based on 3-chloropropionyl chloride (124) as starting material.)

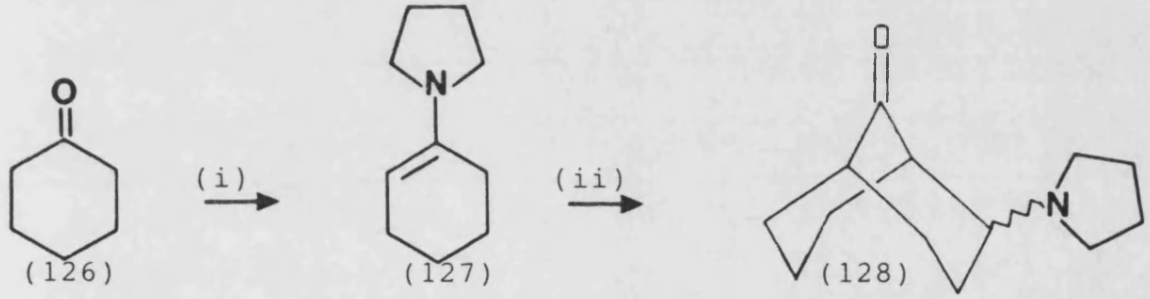


(124) (125) (121)

Reagents: (i) $AlCl_3, CH_2=CH_2$ (ii) H_2O/H^+

Scheme 28

The first reported reaction between an enamine and acrolein to yield a bicyclic compound was that of Stork and Landesman[136] (Scheme 29).

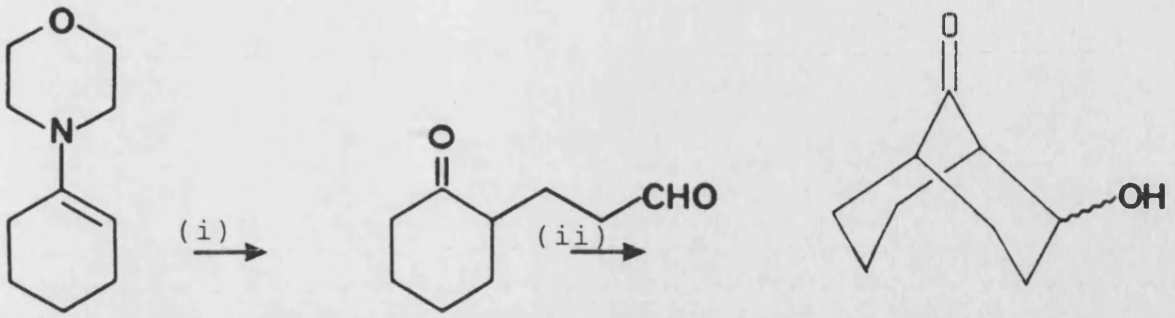


(126) (127) (128)

Reagents: (i) Pyrrolidine, PTSA, Benzene
(ii) Acrolein, Dioxan

Scheme 29

Variations including the isolation of the intermediate 3-(2'-oxycyclohexyl)propanal (130) from the enamine and acrolein have been reported.[137,138] These could then be cyclised by Amberlite IR-120 resin in water to yield the hydroxy ketone (131) (Scheme 30).



(129) (130) (131)

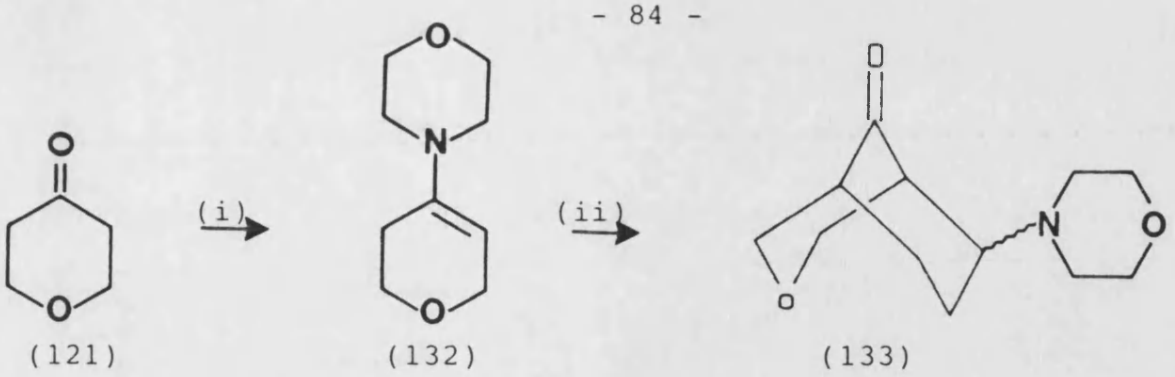
Reagents: (i) Acrolein, 0° (ii) Amberlite IR-120 Resin, H_2O

Scheme 30

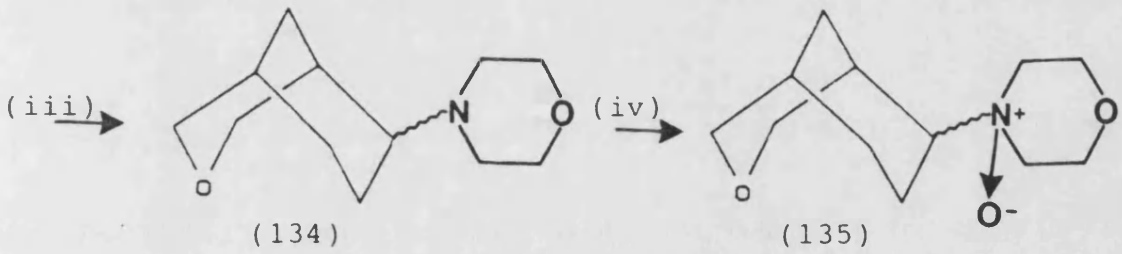
4.2 Synthesis via morpholine enamine and acrolein

Our first approach utilized the morpholine enamine (132), which was obtained in a 90% yield as a white solid (Mp 42-3°). This was reacted with acrolein (Scheme 31) to give 6-morpholino 3-oxabicyclo[3.3.1]nonan-9-one (133) as a mixture of exo and endo isomers in a ratio of approximately 70% to 30% as determined by g.l.c. This compares with the results obtained in similar carbocyclic systems,[139] 70-80% of the α-epimer (exo) and 30-20% of the β-epimer (endo), which approximates to the likely thermodynamic equilibrium.

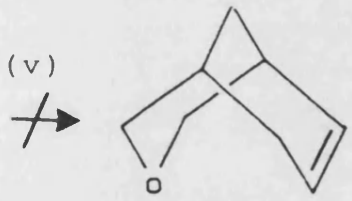
The exo and endo isomers of 6-morpholino 3-oxabicyclo [3.3.1]nonan-9-one (133) were not separated. However, the spectral data were in accord with the required structures. The i.r. spectrum showed one carbonyl stretch (1717cm^{-1}). The ^{1}Hnmr spectrum shows a complex multiplet at δ4.2-3.6 (8H) for the hydrogens adjacent to the ether



(121) (132) (133)



(134) (135)



(28)

Reagents: (i) Morpholine, PTSA, benzene
(ii) Acrolein, benzene
(iii) KOH, Hydrazine hydrate, Digol
(iv) 30% H_2O_2, methanol, ethanol
(v) Pyrolysis

Scheme 31

oxygen. A multiplet at δ2.85 was seen for the CH adjacent to the nitrogen, also, multiplets at δ 2.5 for the CH_2's adjacent to the nitrogen and at δ 2.3-1.8 for the remaining ring protons. In the mass spectrum the molecular ion was seen at m/e 225 indicating that the desired compound had been obtained. However, the base peak was at m/e 126. This will be discussed at a later stage in connection with the mass spectrum of 6-morpholino 3-oxabicyclo [3.3.1]nonane (134). The ketone group of 6-morpholino-3-oxabicyclo[3.3.1]nonan-9-one (133) was removed by a Huang-Minlon[140] modification of the Wolff-Kishner reduction and gave 6 -morpholino 3-oxabicyclo[3.3.1]nonane (134) in 72% yield as a mixture of exo and endo isomers in a ratio of 9:1 as determined by g.l.c. The i.r. spectrum showed the absence of any carbonyl stretch. The ^{1}Hnmr spectrum was essentially the same as that for the oxo-derivative. The mass spectrum showed the molecular ion at m/e 211. As in the oxo-derivative the base peak was at m/e 126. Figure 13 indicates the fragmentation process.

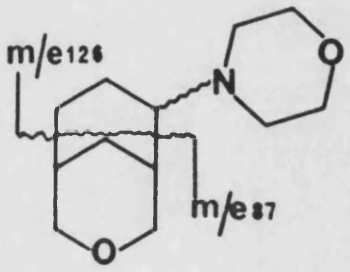


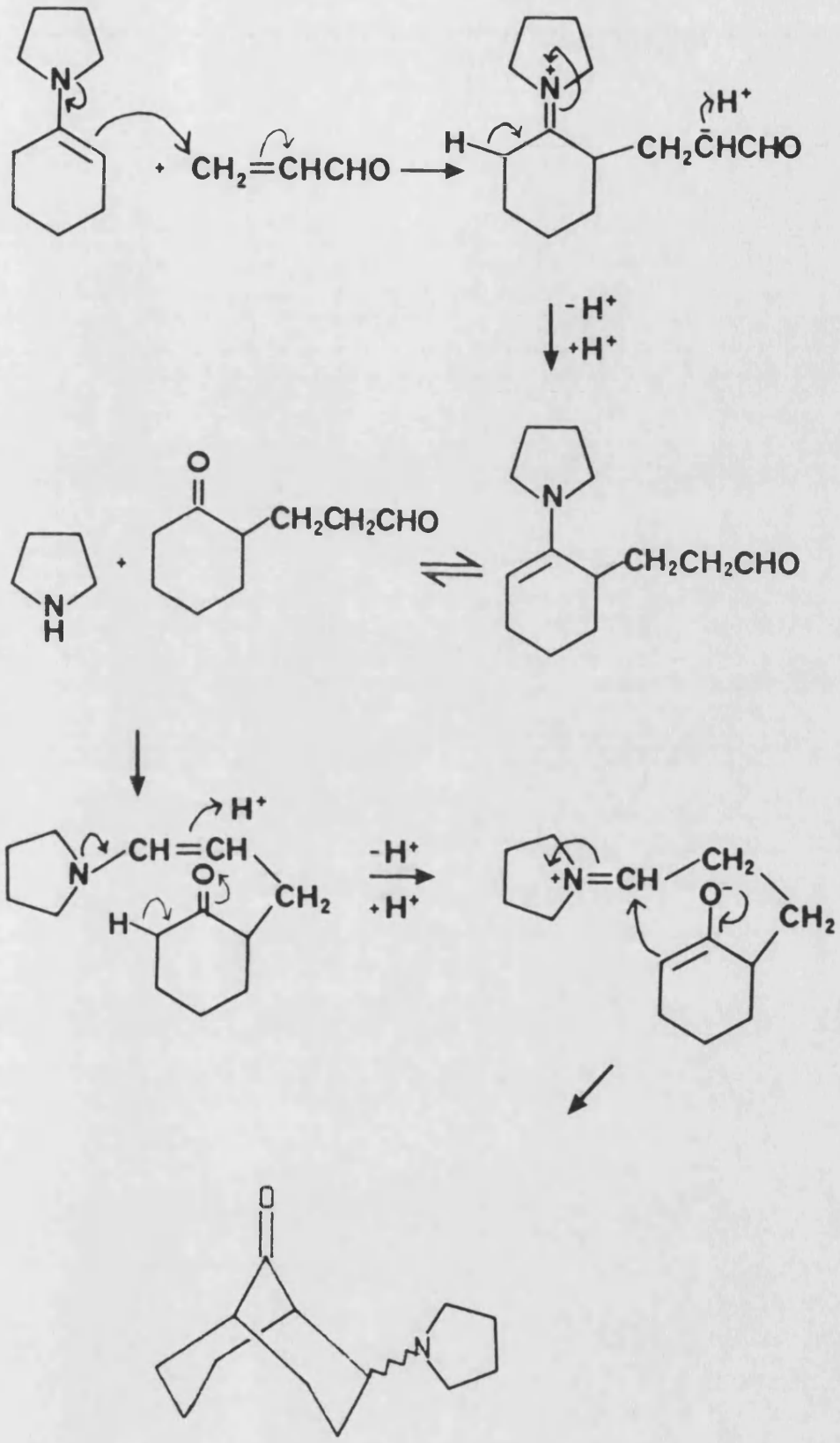
Figure 13

The N-oxide (135) was formed with 30% H_2O_2 in methanol and ethanol. However, pyrolysis of the N-oxide (135) to the alkene (28) was unsuccessful with no identifiable products being obtained. It was then decided to try to effect the Cope elimination using THF with molecular sieves[141] and also with DMSO[141] as these were reported to effect the elimination at lower temperatures, but only starting materials were obtained. Unfortunately the Cope elimination was unsuccessful in our case and it was decided to abandon this approach and try an alternative route, however, still involving the reaction of the enamine of tetrahydro-4H-pyran-4-one with acrolein.

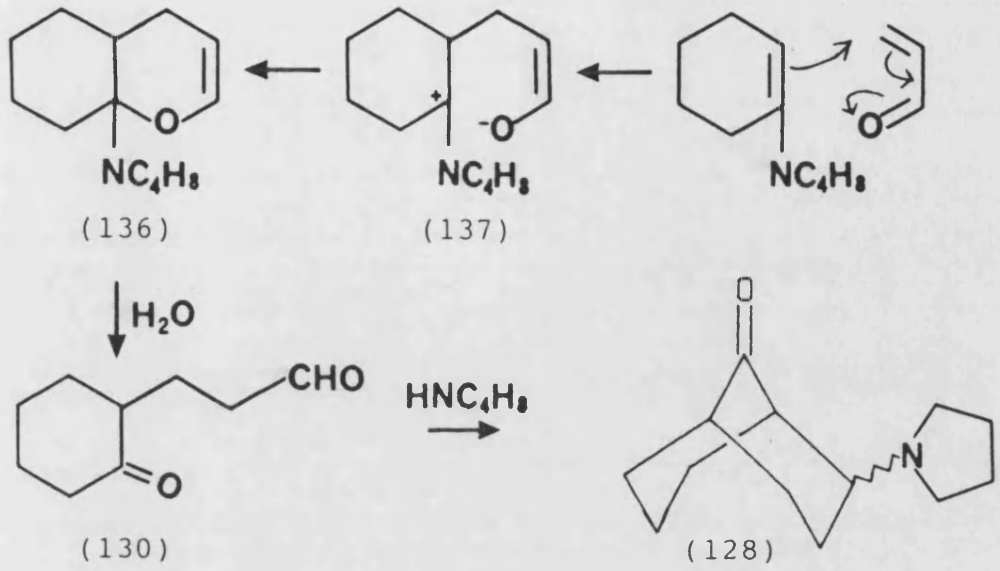
4.3 Mechanism of the enamine reaction with acrolein

The mechanism of formation of the morpholino products (133), which have been regarded[136,139,142] as the expected products between acrolein and a cyclohexanone-enamine has not been fully rationalised.

The standard text book mechanism[143] is illustrated in Scheme 32. However, this mechanism does not fit completely with some of the experimental observations. It has been shown that reaction between the enamine and acrolein at 0° initially leads to an intermediate lacking carbonyl group.[144] It has been postulated that the reaction goes via a dihydropyran (136) and this is formed from a Zwitterion (137).



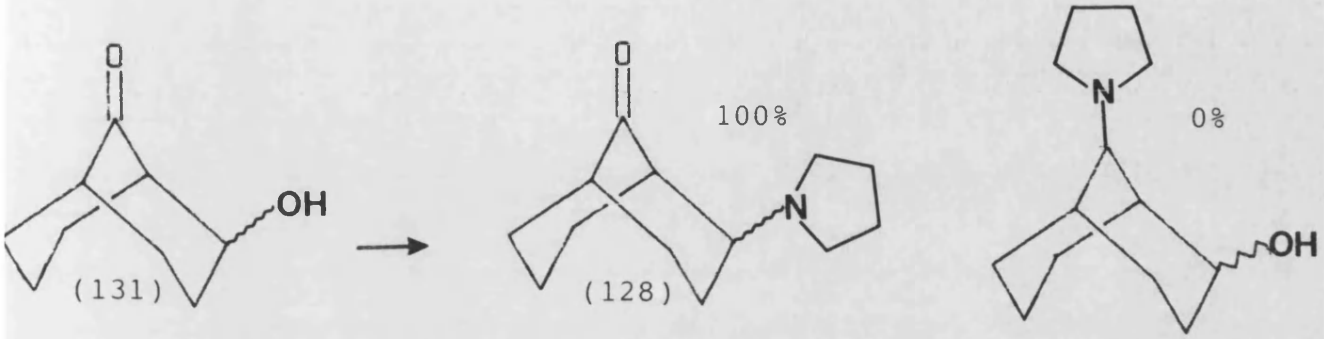
Scheme 32



Scheme 33

The subsequent conversion of the dihydropyran (136) was interpreted as an intermolecular process, since any intramolecular rearrangement would result in a single preferred configuration. As mentioned before a mixture of exo and endo isomers are obtained in agreement with the expected thermodynamic equilibrium. Appleton et al[144] put forward the idea that a small amount of hydrolytic agent would hydrolyse the dihydropyran (136) to a mixture of amine and dicarbonyl compound (130), which would then recyclise to give the expected products (128) (See Scheme 33).

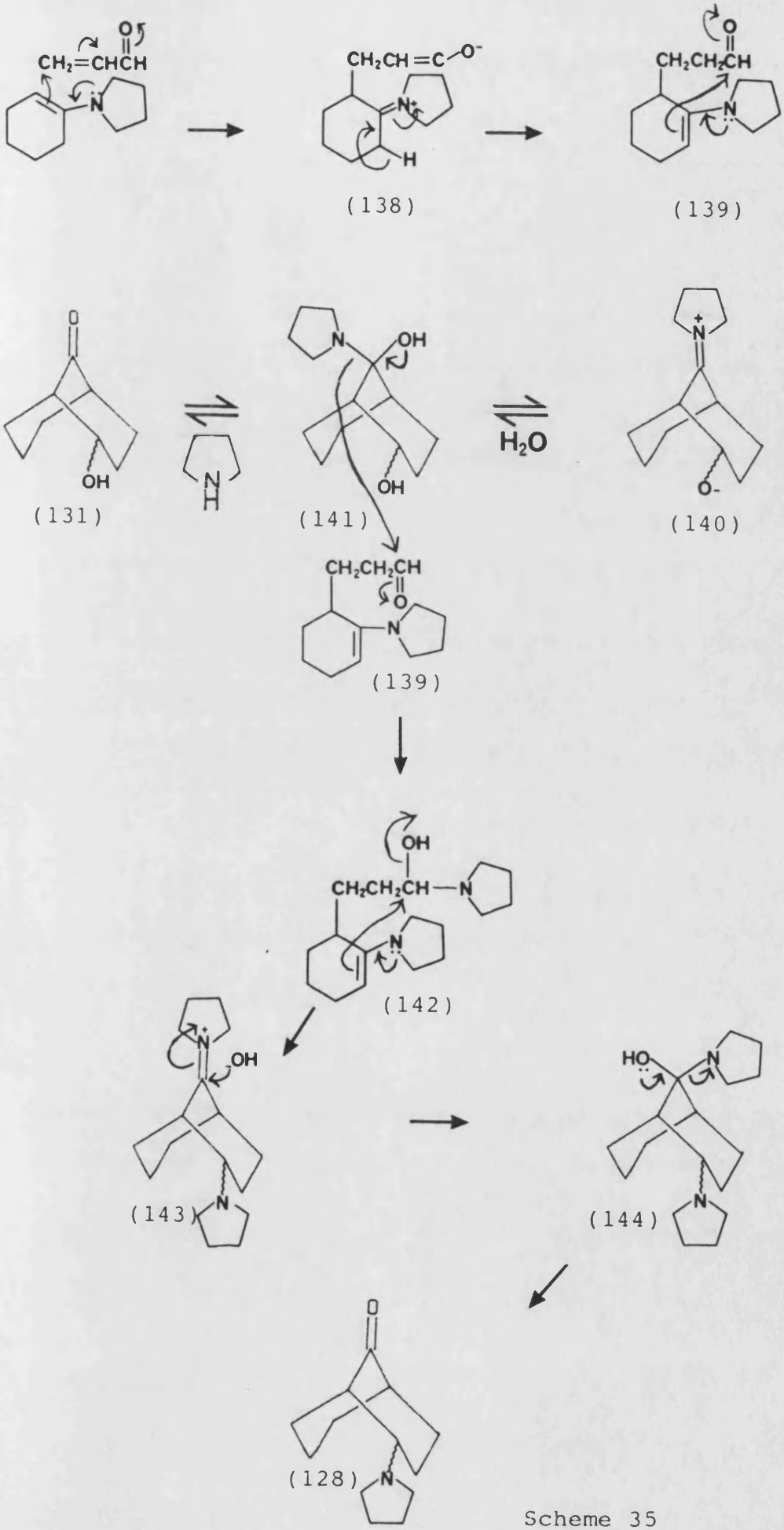
Another interesting feature of this reaction is that the ketols (131) sometimes isolated from this type of reaction, when reacted with pyrrolidine, give the amine products (128) and not those one would expect.[145]



Reagents: (i) Pyrrolidine, benzene

Scheme 34

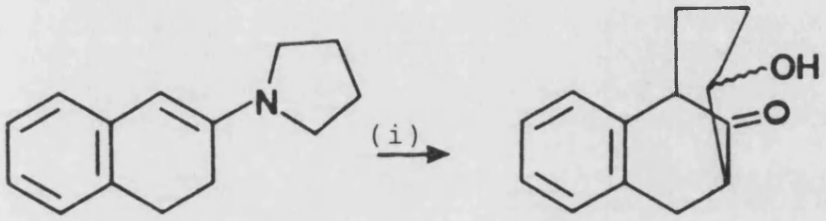
From these observations a mechanism has been postulated[145] which takes into account these experimental findings (see Scheme 35) and does not involve a dihydrogen intermediate. It follows known enamine reaction mechanisms and fits all the required criteria. The intermediates likely to be formed in the cold do not contain carbonyl groups. It involves an intermolecular rather than an intramolecular process (reaction intermediate (141) with another intermediate (139)). This mechanism also indicates a possible pathway for the conversion of ketols (131) to the pyrrolindo compounds (128) on treatment with pyrrolidine.


CH2=CHCH
O
N
CH2CH=C
O-
H
(138)
CH2CH2CH
(139)
OH
(131)
(141)
H2O
(140)
(142)
(143)
HO
(144)
(128)

Scheme 35

4.4 Synthesis via pyrrolidine enamine and acrolein in aq THF

In a procedure developed at Organon[145] in their synthesis of hexahydro-8-hydroxy-5,9-methobenzocycloocten-11-ones (146), it was shown that it was possible to go directly from the enamine to the ketol (146) without prior isolation of the keto-aldehyde which had been the method used previously.[137, 138]



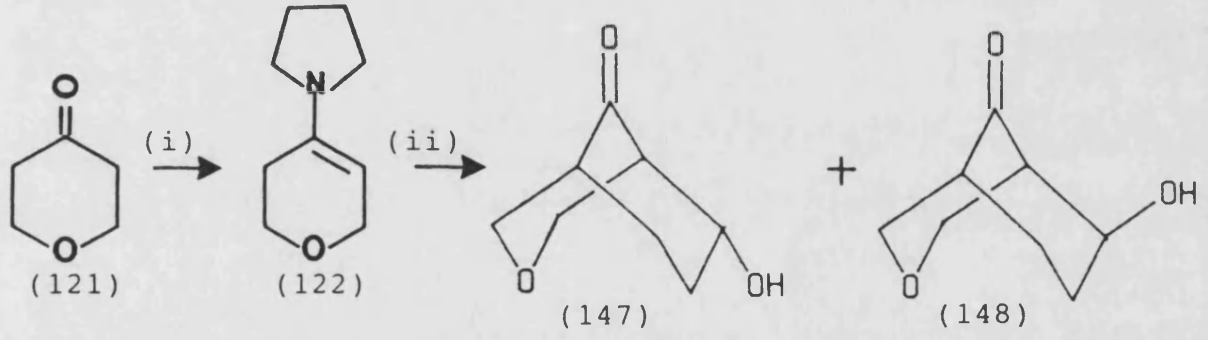
(145) (146)

Reagents: (i) Acrolein, THF(aq)

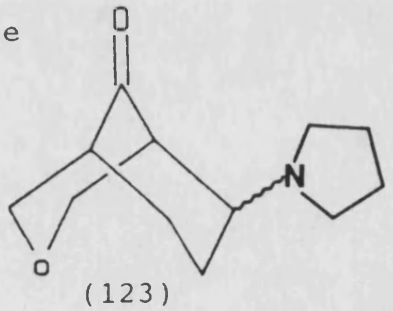
Scheme 36

It was decided therefore to utilize this approach in the synthesis of the 6-hydroxy 3-oxabicyclo[3.3.1] nonan-9-ones (147) and (148). The pyrrolidine enamine of tetrahydro-4H-pyran-4-one (122) was prepared in 90% yield. In the literature method[116] for the preparation of the enamine (122), p-toluene sulphonic acid (PTSA) was used. However, we found that the absence of PTSA made no difference to the yield or any appreciable difference in the rate of reaction and was beneficial as the enamine could be used without any purification. Generally it was used immediately, however, it can be

stored in the fridge under N_2 for several weeks. The i.r. spectrum showed an absence of any carbonyl stretch, and the required double bond stretch (1645cm^{-1})was present. The ^{1}Hnmr spectrum showed a triplet at δ4.6, J=3Hz for H-3, multiplets at δ4.2 and 3.8 for H-2 and H-5, a multiplet at δ2.81 for pyrrolidine NCH_2 protons and at δ2.2-1.8 for the remaining protons. The enamine was reacted with acrolein in THF (aq) to give 6-hydroxy 3-oxabicyclo[3.3.1]nonan-9-one as a mixture of exo (147) and endo (148) isomers in 60% yield in a 1:1 ratio as determined by g.l.c. These were separated using a Chromatotron (centrifugally accelerated chromatography). On basification of the acid aqueous layer, a small amount (approximately 5%) of exo and endo 6-pyrrolidinyl 3-oxa bicyclo[3.3.1]nonan-9-one (123) was isolated.



Reagents: (i) Pyrrolidine, Benzene
(ii) Acrolein, THF(aq)



(123)

Scheme 37

The exo (147) and endo (148) isomers were identified by their spectral data. The i.r. spectra were identical, with both showing hydroxyl (3460, 3450) and carbonyl (1720cm^{-1}) functions. The mass spectra were also essentially the same with the fragmentations shown in the figure 14, the most important fragmentations being loss of the hydroxy function to give the base peak at m/e 138 and then loss of an oxygen containing fragment which is common in 3-oxabicyclo[3.3.1]nonanes and can be one or more of the following: CH_2O, CH_2OH, CH_3O, CH_3OH and CH_3OCH_3.

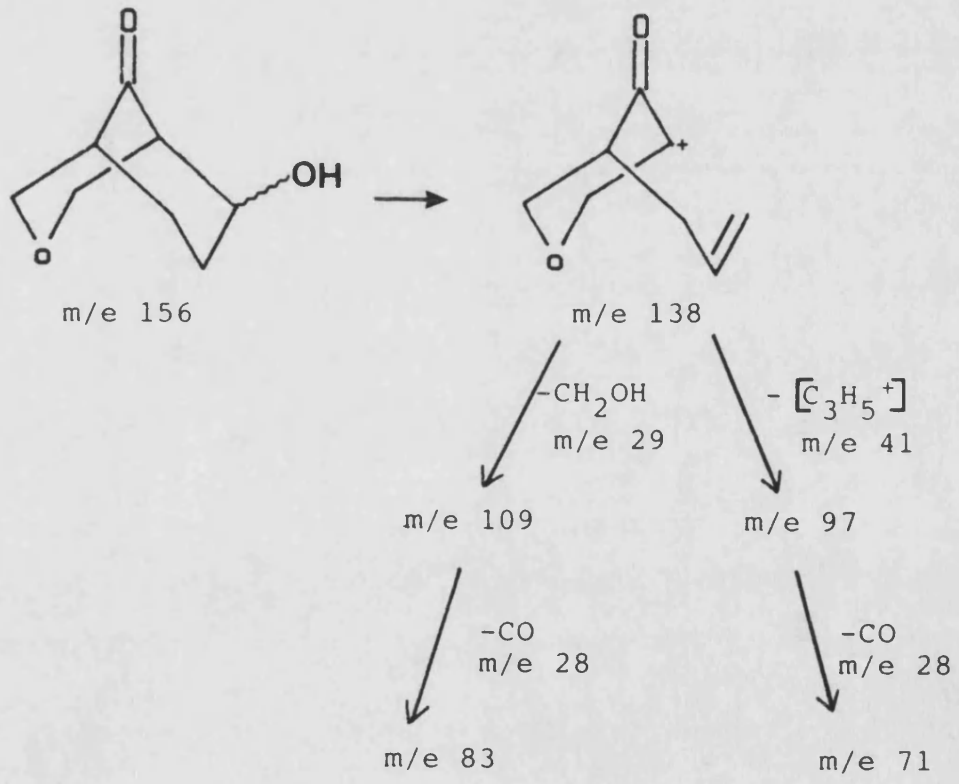


Figure 14

The real difference between the two isomers was apparent from their nmr data.

4.5 ^{1}Hnmr study of exo and endo 6-hydroxy 3-oxabicyclo [3.3.1]nonan-9-one (147) and (148)

At this point we carried out a detailed analysis of the ^{1}Hnmr spectra of the two hydroxy isomers, in order to rigorously elucidate their structures. To achieve this a number of decoupling experiments were performed

The exo and endo isomers could readily be identified. This was achieved by comparison of the methine protons associated with the hydroxy groups. We assume that a low field methine indicates an equatorial hydrogen, and consequently an axial hydroxy and therefore the endo isomer. In the endo isomer the methine is seen at δ4.6 whereas in the exo isomer it is seen at δ4.11. The endo isomer also showed a less complicated CH_2OCH_2 system with no 'W' coupling present. 'W' coupling (^{4}J) is observed in saturated compounds, where the C-H and C-C bond exist in the form of a 'W' arrangement (figure 15).

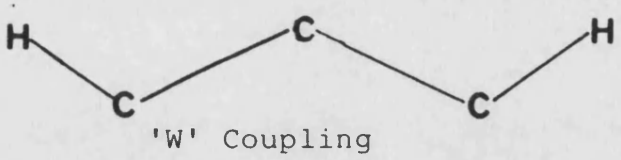
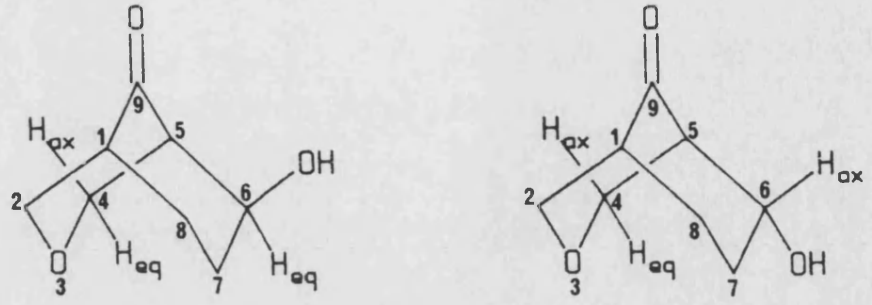


Figure 15

The presence of ^{4}J coupling is important in the assignment of stereochemistry in the exo and endo derivatives. Only the axial methine (exo isomer) can couple with H_4 axial to give a 'W' coupling of the

magnitude of 1.1Hz (figure 16).



ENDO
no 'W' Coupling
between H_6eq and H_4ax

EXO
'W' Coupling between
H_6ax and H_4ax

Figure 16

The difference manifests itself in the spectra by giving for the H-4axial in the exo isomer a doublet of quartets whereas for the endo isomer only a doublet of doublets is seen (see spectra). The ^{1}Hnmr data for the exo and endo isomers is shown in table 3. The spectra were assigned by using decoupling experiments. In both isomers irradiation was carried out on the methine proton by the hydroxy (H-6) and on one of the bridgehead methines. In the case of the exo compound the C-1 methine, and for the endo isomer the C-5 methine were irradiated.

In the exo isomer, irradiation at δ4.11 caused simplification from a doublet of quartets to a doublet of doublets at δ3.73 indicating the 'W' coupling and therefore the H-4ax proton. It simplifies at δ2.53 indicating the C-5 methine, and also at δ2.02 going from a quintet to a quartet indicating the H-7ax proton.

There is also a small change at δ2.12 showing the presence of a 'W' coupling between H-6ax and H-8ax. Irradiation at δ2.35 causes simplification at δ4.18 and 3.92 going from a doublet of triplets to a doublet of doublets and from this it may be deduced that these two resonances are due to H-2eq and H-2ax. Simplification at δ2.53 indicates for the H-5 methine a 'W' coupling across the smallest bridge, and at δ2.11 and 1.83 showing the H-8eq and H-8ax protons.

In the endo isomer decoupling at δ4.55 causes simplification at δ2.48 indicating the H-5 methine. Irradiation at δ2.48 simplifies the spectrum at δ4.18 and 3.83 showing the H-4eq and H-4ax protons. The methine at δ4.55 is sharpened. The methine at δ2.38 is too close to the irradiated peak to see the 'W' coupling.

The protons next to the ether oxygen were also assigned via their geminal coupling constants (Table 4) and these agreed with the assignments made from the decoupling experiments.

J_{1-2ax} and J_{4ax-5} are diagnostic for the conformation of the tetrahydropyran ring. As the values are small (<4Hz), this shows that the tetrahydropyran ring exists predominantly (>90%) in the chair conformation. J_{5-6ax} and J_{1-8ax} give the conformation in the other ring. Unfortunately from the spectra we were unable to determine these.

Table 3 ^{1}Hnmr chemical shifts for exo and endo 6-hydroxy 3-oxabicyclo[3.3.1]nonan-9-one

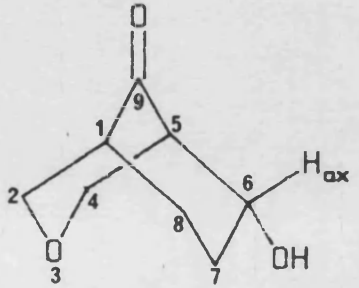
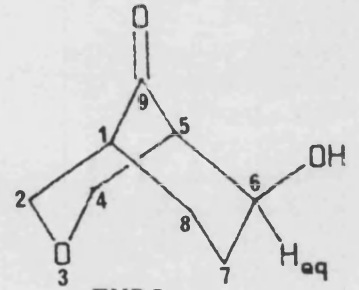
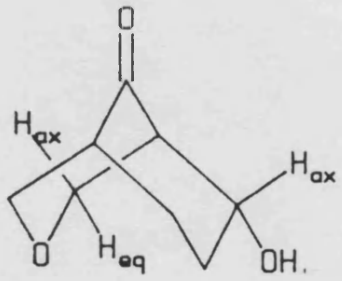
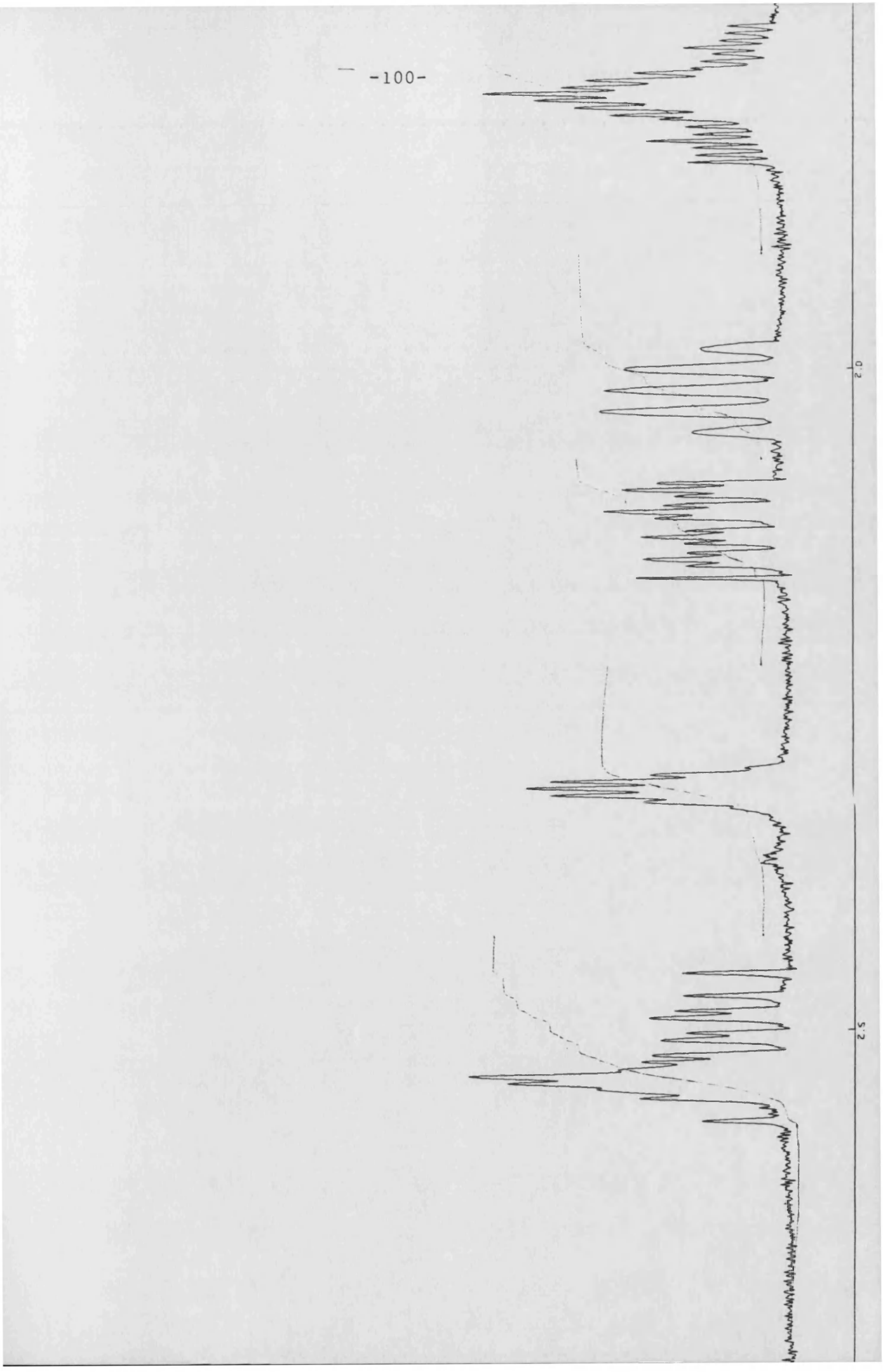
Compound	Chemical shift δ_H (PPM)											
	H-1	H-2eq	H-2ax	H-4eq	H-4ax	H-5	H-6	H-7eq	H-7ax	H-8eq	H-8ax	-OH
 EXO	2.35	4.18	3.92	4.6	3.73	2.53	4.11	2.50	2.02	2.11	1.83	1.79
 ENDO	2.38	4.27	3.88	4.18	3.83	2.48	4.55	2.75	2.38	2.10	1.74	1.72

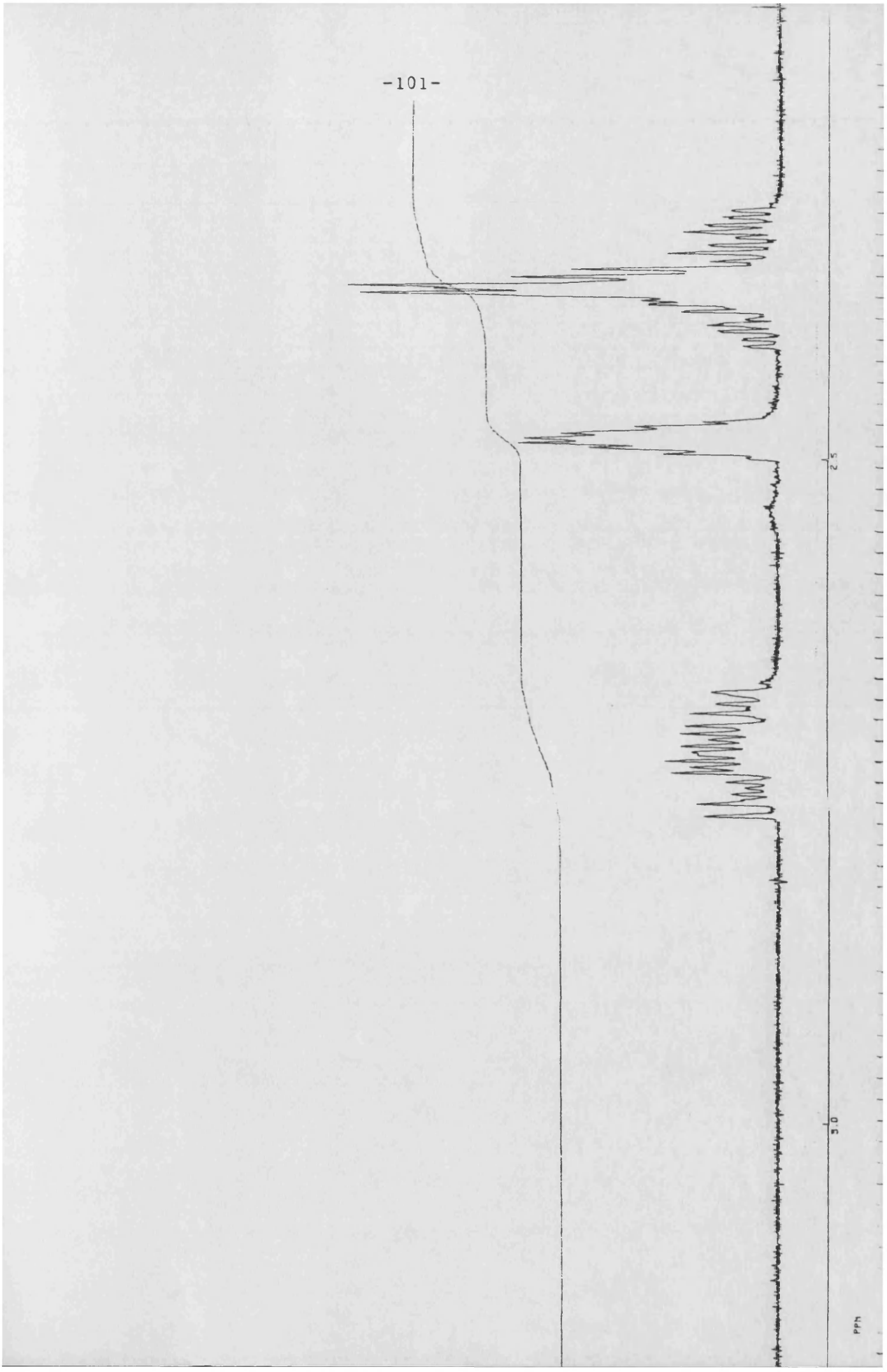
Table 4 ^{1}Hnmr Coupling Constants for exo and endo 6-hydroxy 3-oxabicyclo[3.3.1]nonan-9-ones

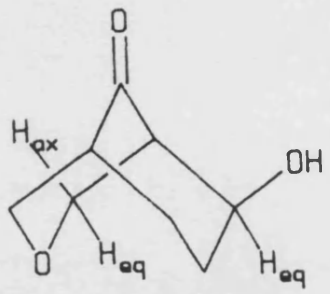
	Coupling Constant J(Hz)		
Compound	J_{GEM}	J_2	J_3
Exo	J_{2eq-ax} = 11.32 J_{4eq-ax} = 11.56	J_{1-2eq} = 1.6 J_{1-2ax} = 2.1 J_{4eq-5} = 1.48 J_{4ax-5} = 2.4	$J_{4ax-6ax}$ = 1.1
Endo	J_{2eq-ax} = 11.28 J_{4eq-ax} = 11.72	J_{1-2eq} = 1.6 J_{1-2ax} = 2.1 J_{4eq-5} = 1.48 J_{4ax-5} = 2.8	



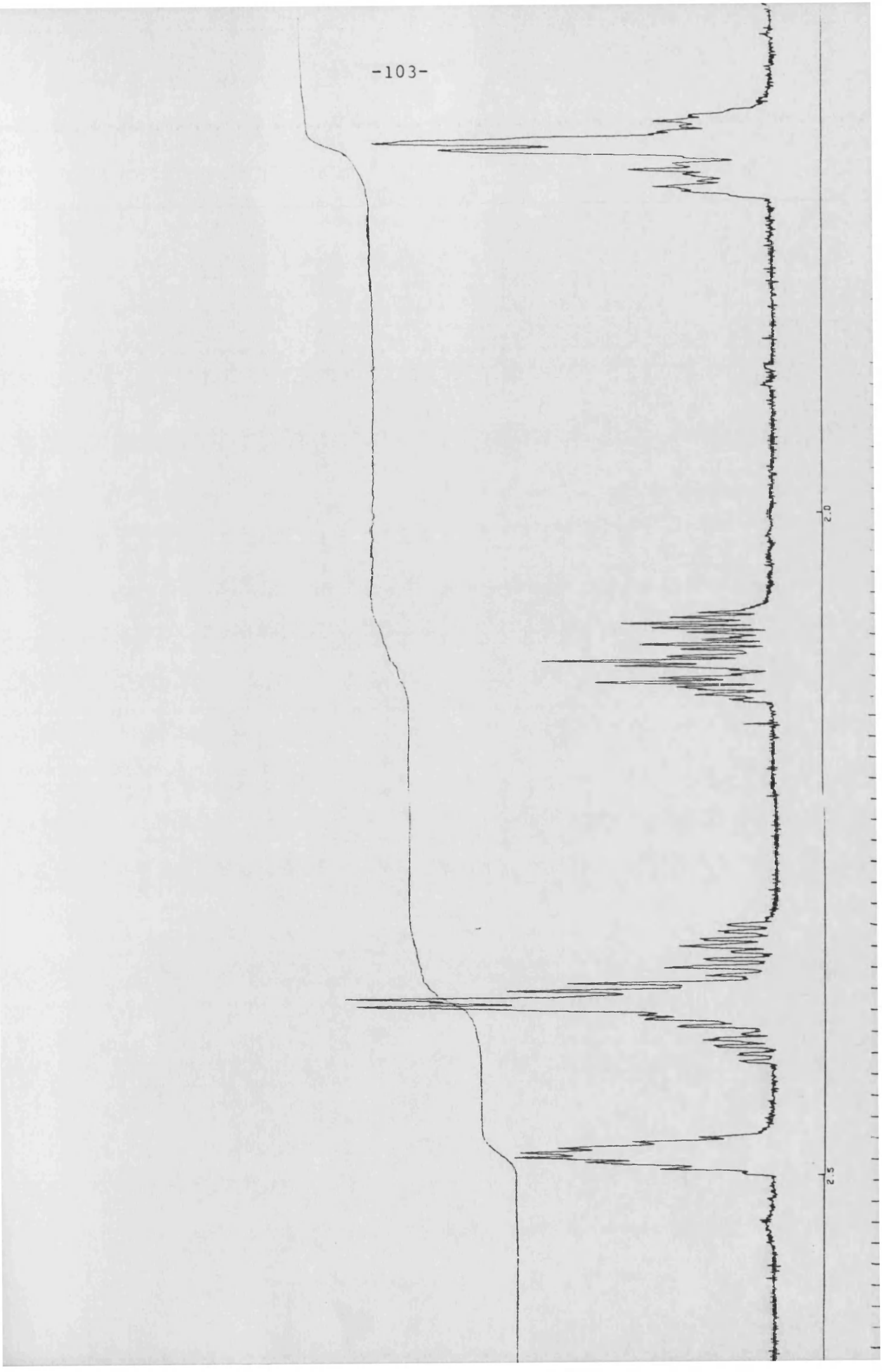
Exo isomer


2.0
2.5


2.5
3.0
PPM

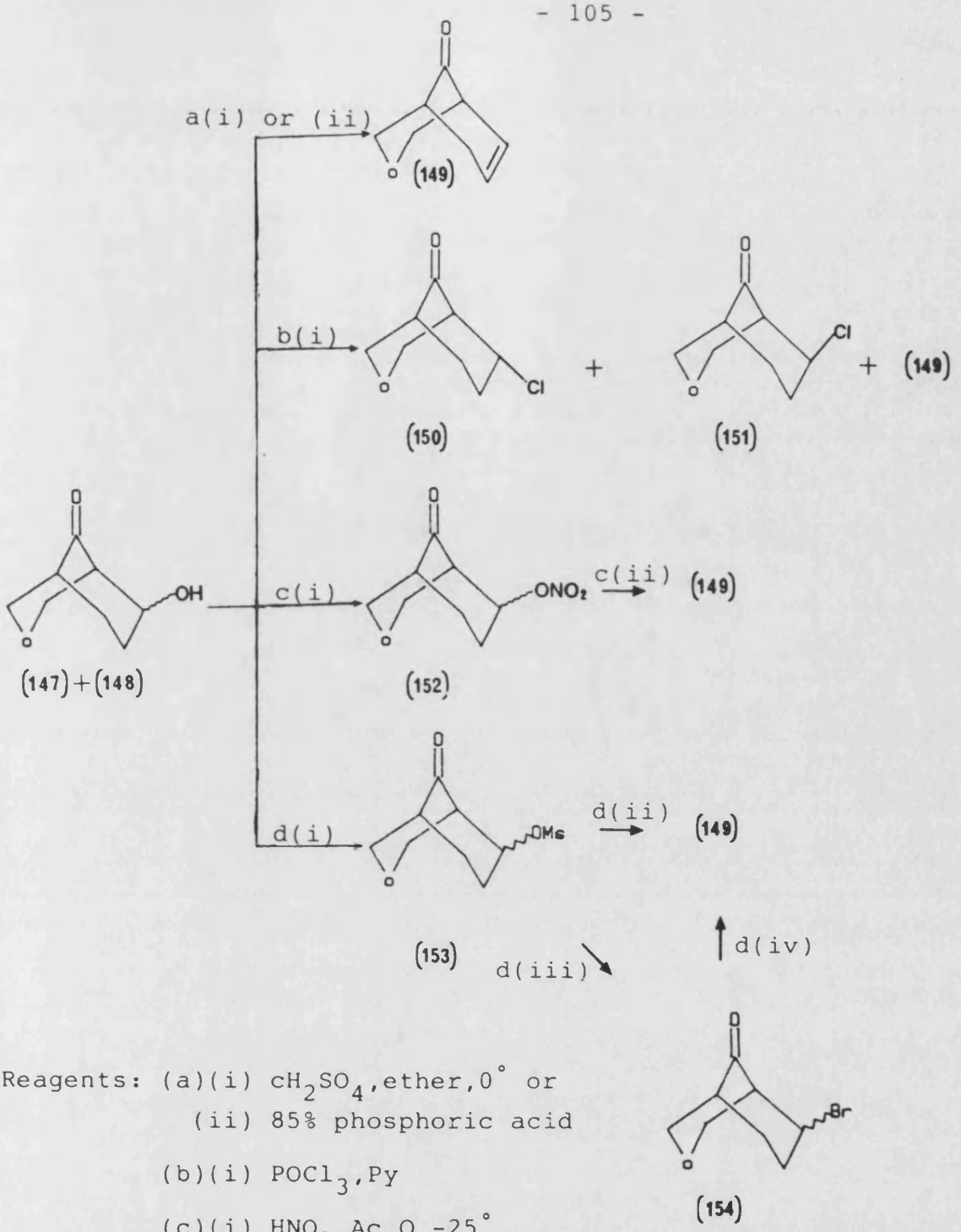


Endo isomer


2.0
2.5

4.6 Synthesis of 3-oxabicyclo[3.3.1]non-6-en-9-one(149)

In our approach to the synthesis of 3-oxabicyclo [3.3.1]non-6-ene (28) it was hoped to dehydrate the keto-alcohols (147) and (148) followed by a Huang-Minlon reduction of the resulting 3-oxabicyclo[3.3.1]non-6-en-9-one (149). However, the dehydration of (147) and (148) did not prove to be an easy matter. Simple acid dehydration using cH_2SO_4 in ether[146] gave the desired compound in a yield of only 15%. Using 85% phosphoric acid also gave a messy reaction mixture and a correspondingly low yield. An explanation for this is that these types of acid dehydration go via cations, which may cause skeletal rearrangements. No other identifiable products were isolated from the reaction mixture. Reaction with phosphorus oxychloride and pyridine[147] gave a mixture of the exo and endo 6-chloro 3-oxabicyclo[3.3.1]nonan-9-ones (150) and (151) and the alkene (149). These were separated by medium pressure chromatography. The stereochemistry was assigned by the fact that the endo isomer had a low field methine proton (C<u>H</u>Cl, δ4.82), whereas in the exo isomer the corresponding methine proton was at a higher field (C<u>H</u>Cl, δ4.35). The endo isomer also showed a less complicated CH_2OCH_2 system. In the endo isomer H_4 axial is a doublet of doublets (δ3.86) whereas the exo isomer H_4 axial is a doublet of triplets (δ3.79). There is evidence of 'W' coupling in the exo, but not the endo isomer. The ^{13}Cnmr spectra agreed with these assignments (see section 4.11), the two important



Reagents: (a)(i) cH_2SO_4,ether,0° or
(ii) 85% phosphoric acid

(b)(i) $POCl_3$,Py

(c)(i) HNO_3,Ac_2O,-25°
(ii) LiCl,Li_2CO_3,N-methyl pyrrolidone

(d)(i) MsCl,Et_3N,DCM (ii) Collidine,Δ
(iii) LiBr,Acetone (iv) LiBr,Li_2CO_3,DMF

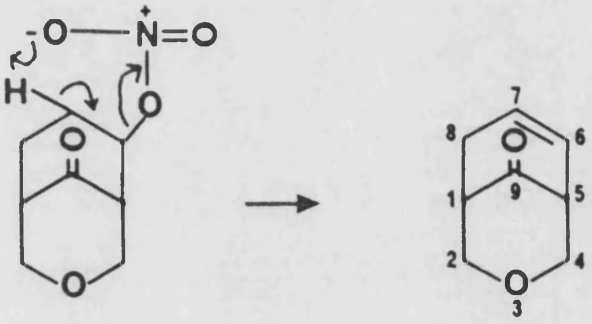
Scheme 38

differences being the resonances at carbons 4 and 6. This will be discussed in section 4.11. The mass spectra of the two isomers were slightly different. They both gave molecular ions at m/e 176/174. However, they had different base peaks, that for the exo isomer being at m/e 138 and for the endo isomer at m/e 55.

Mesylation of the ketoalcohols (147 and 148) afforded the mesylates (153) in 86% yield as a mixture of exo and endo isomers. These were not separated. The ^{1}Hnmr spectrum showed the equatorial methine (δ5.2) of the endo isomer and the axial methine (δ4.3) of the exo isomer. Elimination of the mesylates (153) in refluxing collidine afforded the desired alkene (149) in 42% yield. Elimination in glacial acetic acid-sodium acetate-acetic anhydride[148] gave the alkene (149) in 27% yield. Conversely, bromination of the mesylate with LiBr in acetone and elimination of the bromo compounds (154) with Li_2Co_3-LiBr in DMF[149] gave the desired compound (149) in 67% yield.

By far the most successful method was by the elimination of exo and endo 6-nitrooxy 3-oxabicyclo[3.3.1] nonan-9-one (152), which was formed by the reaction of the ketol-alcohols (147) and (148) with fuming HNO_3 and acetic anhydride.[150] The ^{1}Hnmr spectrum showed the equatorial proton (δ5.62) of the endo isomer and the axial methine proton (δ5.25) of the exo isomer. The elimination was performed using LiCl-Li_2CO_3 and N-methylpyrrolidone[151] and this gave the required alkene

(149) in 70% yield. The success of this reaction in comparison with the others is that it probably goes via a cyclic transition state (figure 17) with syn elimination. In this type of reaction there is no possibility to form potentially rearrangeable cations. Consequently formation of the nitrate ester (152) and subsequent elimination is our preferred method for the formation of 3-oxabicyclo [3.3.1]non-6-en-9-one (149).



(149)

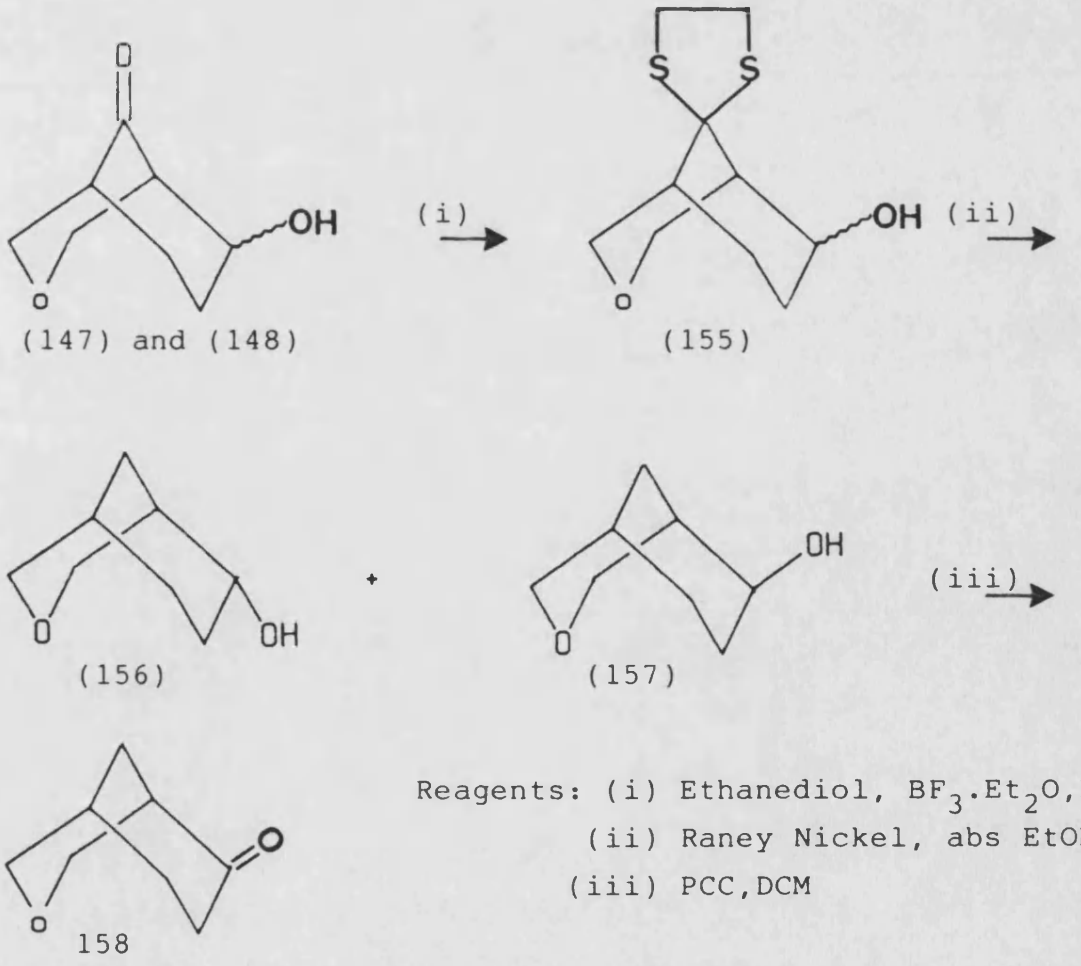
Figure 17

The i.r. spectrum showed the double bond (3031,=CHSt, 1648cm^{-1}C=CSt) and the carbonyl (1728cm^{-1}). The ^{1}Hnmr spectrum exhibits a doublet of triplets at δ6.01 (J_1=9.5Hz, J_2=3.3Hz) (H-6) and a quartet of triplets at δ5.7 (J_1=9.5Hz, J_2=6Hz and J_3=1.9Hz) (H-7). A doublet of triplets at δ4.15 and δ3.94 appeared for H_{2eq} and H_{4eq} and a doublet of doublets at δ3.79 and δ3.71 for H_{2ax} and H_{4ax}. A multiplet at δ2.81 (3H) was assigned to H-8 and the bridgehead hydrogen nearest the double bond (H-5). The other bridgehead hydrogen appeared at δ2.54. The structure was confirmed by the ^{13}Cnmr spectrum: 210.58 (s,C-9), 131.01 (d,C-6), 125.08 (d,C-7), 76.81(t,C-4), 72.25(t,C-2), 50.16 (d,C-5), 48.45(d,C-1), 36.58(t,C-8). The mass spectrum

gave a molecular ion at m/e 138, which was also the base peak. The other fragmentations are those normally associated with this type of ring system.

4.7 Synthesis of 3-oxabicyclo[3.3.1]nonan-6-one (158)

The synthetic strategy was to take the keto-alcohols (147) and (148), remove the keto group and then oxidise the alcoholic function. For removal of the keto group the Huang-Minlon method was avoided due to the possibility of effecting a reverse aldol reaction due to the presence of the β-hydroxy carbonyl grouping. The method chosen was to form the dithiolane (155) and then subsequent desulphurisation to afford the hydroxy compounds (156) and (157).



Reagents: (i) Ethanediol, $BF_3.Et_2O$, DCM
(ii) Raney Nickel, abs EtOH
(iii) PCC, DCM

Scheme 39

The dithiolane (155) was formed using a modification of the existing method.[152] It was found that using a non-aqueous work up, increased yields could be obtained by as much as 30%. Normally, the reaction is worked up with 5% NaOH (Aq), which is used to remove the excess ethanedithiol. In our case the reaction mixture was concentrated and then chromatographed directly to give the dithiolane (155) in 86% yield. When an aqueous work up was used, yields of around 50% were obtained. This is due to high water solubility of these 3-oxabicyclo[3.3.1] nonan-6-ols, and in reactions involving these types of compounds we tried as much as possible to keep to non-aqueous work ups.

The dithiolane (155) was obtained as a mixture of exo and endo isomers clearly seen in the ^{13}Cnmr spectrum with the peak of one isomer being mirrored by the peak of the other isomer. However, they appeared as only one spot on t.l.c. (PE/EA,5:1) and consequently no attempt was made to separate the isomers. The i.r. spectrum showed the absence of any carbonyl stretch. The dithiolane was shown in the ^{1}Hnmr spectrum by a multiplet between δ3.35-3.13 integrating to four protons. The mass spectrum gave a molecular ion at m/e 232. The base peak was at m/e 214, due to loss of water from the molecular ion.

Desulphurisation was effected using hydrazine hydrate (98%) and KOH in trigol at 135° ,[153] but this gave extremely low yields ($\sim$30%). Liquid NH_3/Na[154] only gave marginally better yields ($\sim$40%) and Raney Nickel in absolute

ethanol[155] gave by far the best yield (∿70%). The problem associated with the first two methods is the high water solubility of the products, whereas the third method is a non-aqueous method and consequently gives a greater yield. However, since a large excess of Raney Nickel is required (7g/g of substrate), it is difficult to use in large-scale preparations. This was primarily the reason for trying the other methods. Although they are easier to perform on a larger scale, the yields are considerably reduced.

Exo and endo 3-oxabicyclo[3.3.1]nonan-6-ols (156) and (157) were obtained in an approximately 1:1 ratio and were separated by flash chromatography. These were identified using ^{1}Hnmr and ^{13}Cnmr spectroscopy. In the ^{1}Hnmr spectra, the methine associated with the hydroxy group was at δ4.09 in the endo isomer whereas in the exo isomer it was at higher field (δ3.98). The endo isomer also showed a less complicated CH_2OCH_2 system. In the ^{13}Cnmr spectrum the carbon associated with the hydroxy group was at lower field for the exo isomer (δ72.91), the endo isomer being at δ70.58. The other main difference was at C-4, the exo isomer being at a lower field (δ66.48) than the endo isomer (δ69.56). The mass spectra were essentially the same, each having molecular ions at m/e 142 and base peaks at m/e 79. The main fragmentations in the spectra being the loss of water and other oxygen containing fragments.

The exo and endo alcohols (156) and (157) were oxidised by pyridinium chlorochromate (PCC)[156] to give 3-oxabicyclo

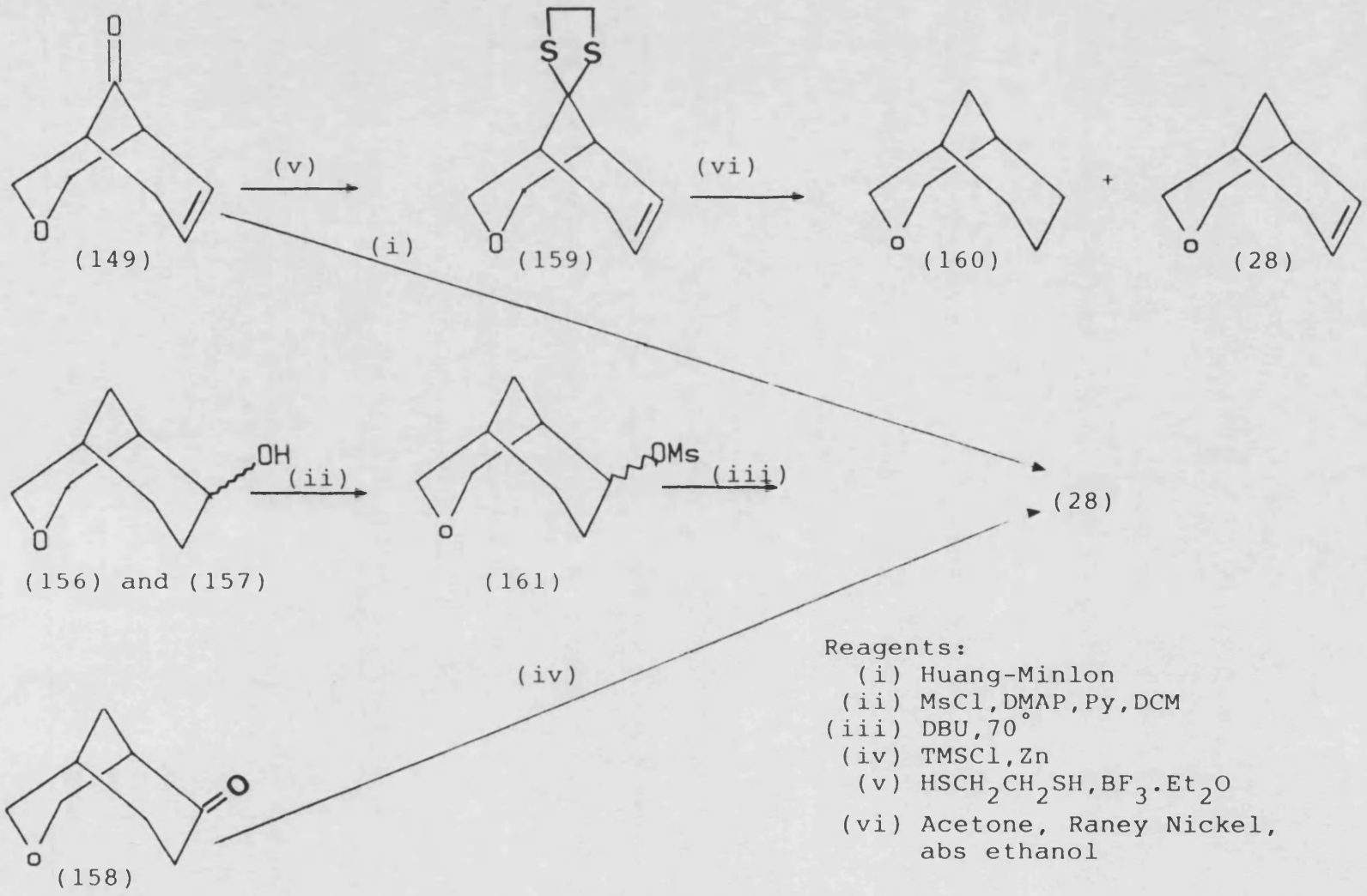
[3.3.1]nonan-6-one (158) in a 70% yield. The oxidation product had an M^{+1} peak at m/e 141 and a ^{13}Cnmr resonance at δ213.86 together with a strong absorption at ν_{max} 1705cm^{-1} in the i.r. showing it to be the desired compound.

4.8 Synthesis of 3-oxabicyclo[3.3.1]non-6-ene (28)

The synthesis of 3-oxabicyclo[3.3.1]non-6-ene (28) was achieved in a number of ways (scheme 40) all involving different starting materials. The first approach involved the Huang-Minlon[140] reduction of 3-oxabicyclo[3.3.1]non-6-en-9-one (149). This gave the desired compound in a very low yield ~10%. A possible reason for the low yield is that these types of compounds are too sensitive to be able to withstand such harsh conditions.

The second approach involved mesylation of 3-oxabicyclo [3.3.1]nonan-6-ols (156) and (157) and elimination of the mesylates (161) with 1,8-diazobicyclo[5.4.0]undec-7-ene (DBU)[157] at 70° with no solvent present to give the desired compound in 39% yield.

The third approach involved 3-oxabicyclo[3.3.1]nonan-6-one (158) which was directly reduced to the cycloalkene by treatment with chlorotrimethyl silane and zinc,[158] and gave the desired compound in a 41% yield. The mechanism postulated is via an ylide - stabilised organozinc carbenoid intermediate, which can undergo insertion into a neighbouring C-H bond.



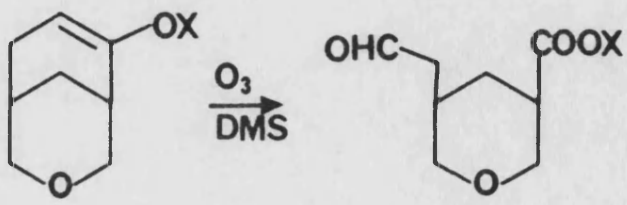
Reagents:
(i) Huang-Minlon
(ii) MsCl, DMAP, Py, DCM
(iii) DBU, 70°
(iv) TMSCl, Zn
(v) $HSCH_2CH_2SH, BF_3.Et_2O$
(vi) Acetone, Raney Nickel, abs ethanol

Scheme 40

The fourth approach involved the attempt to selectively remove the thioacetal of 3-oxabicyclo[3.3.1] non-6-en-9-one (159) without reducing the double bond. It was hoped to achieve this by refluxing the Raney nickel in acetone prior to use and hence deactivating it. Unfortunately, on reduction a mixture of 3-oxabicyclo [3.3.1]non-6-ene (28) and 3-oxabicyclo[3.3.1]nonane (160) was obtained. The i.r. spectrum of 3-oxabicyclo[3.3.1] non-6-ene (28) showed the double bond at 1640cm^{-1}. The ^{1}Hnmr spectrum showed multiplets at δ5.9 and 5.6 (H-6 and H-7 respectively). The mass spectrum gave a molecular ion peak at m/e 124.

4.9 Synthesis of enol ethers of 3-oxabicyclo[3.3.1]nonan-6-one (158)

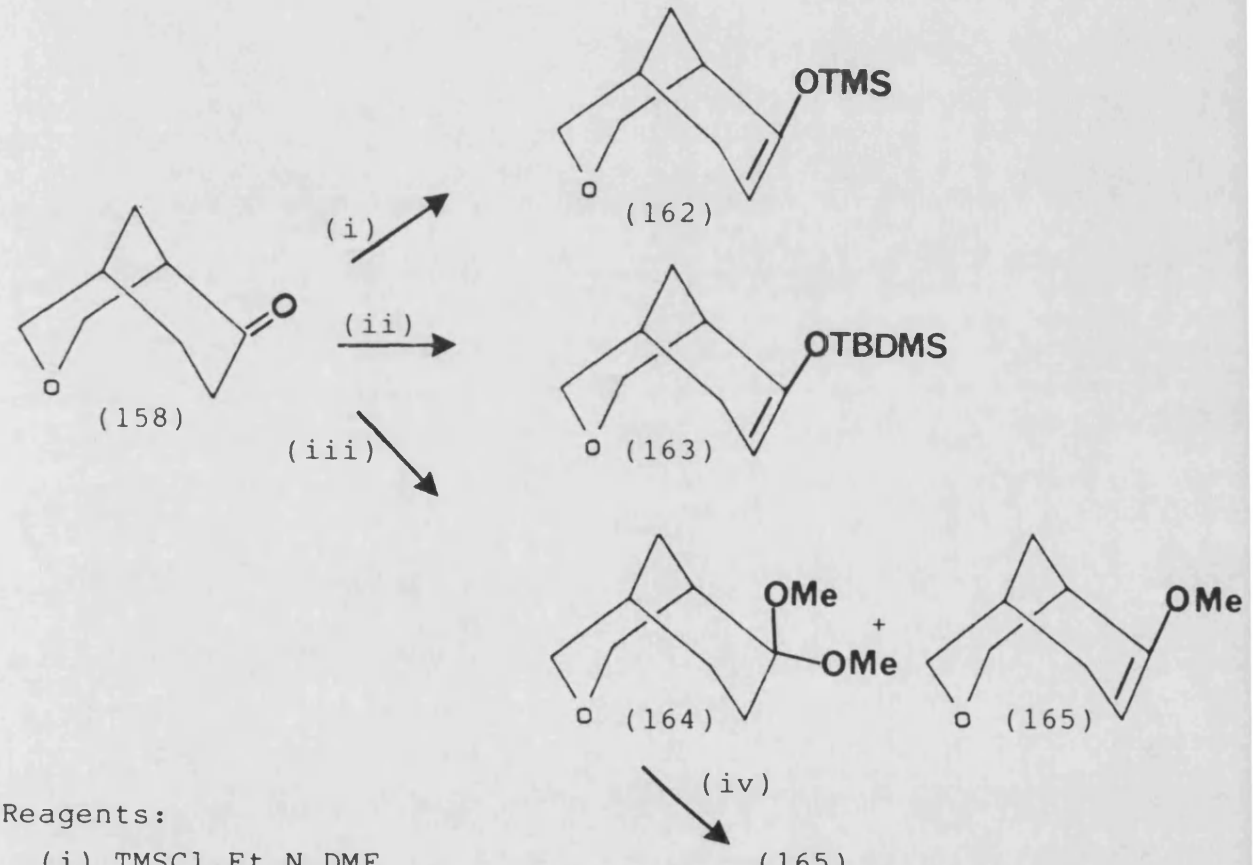
The idea behind the synthesis of the enol ethers was that they would provide, once ozonolysed, a way of differentiating between the C-3 and C-5 side chains in the tetrahydropyran as they would be in different oxidation states, one as the aldehyde, the other as the carboxylic acid or ester (figure 18).



X = TMS, TBDMS or Me

Figure 18

The TMS enol ether (162) was synthesised using the method of House et al[159] and was obtained in a yield of 56%. The i.r. spectrum showed the double bond stretch at 1650cm^{-1}. The ^{1}Hnmr showed a triplet at δ4.8 (J=3Hz) for the proton associated with the double bond and a singlet at δ0.15 for the trimethyl silyl group. The mass spectrum gave a molecular ion at m/e 212.



Reagents:

(i) TMSCl, Et_3N, DMF
(ii) TBDMS triflate, 2,6-lutidine, DCM
(iii) 2-methoxypropene, PTSA, DMF
(iv) PTSA, Trimethylorthoformate

Scheme 41

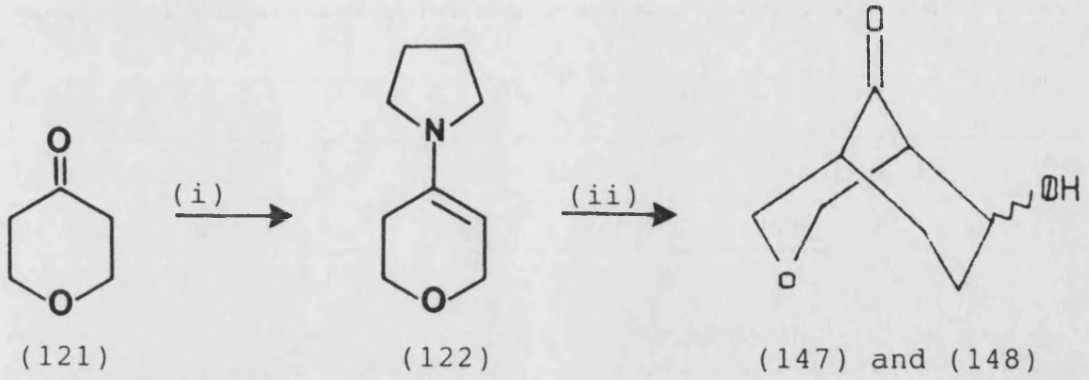
The TBDMS enol ether (163) was synthesised using a method of Clark and Heathcock[160] using LDA, HMPT and TBDMSCl and was obtained in a yield of 58%. However, it was obtained in much higher yield (95%) using the method of Mander and Sethi,[161] which uses TBDMS triflate and 2,6-lutidine. One limiting factor for this reaction is the expense of TBDMS triflate,which requires the use of two equivalents. The i.r. spectrum showed the required double bond stretch at 1660cm^{-1}. The ^{1}Hnmr spectrum showed a triplet at δ5(J=3Hz) for the proton associated with the double bond. Doublets were seen at δ3.81 (H_{4eq}),3.75 (H_{2eq}), 3.65(H_{4ax}) and doublet of doublets at δ3.45(H_{2ax}) which were assigned by comparison of their geminal coupling constants. The H-5 bridgehead proton resonates as a doublet of doublets. Multiplets were seen at δ2.10-2.0 for the C-8 hydrogens and at δ1.9 for the remaining ring protons. The two singlets at δ0.95 and δ0.15 were attributed to $(CH_3)_3CSi$ and $(CH_3)_2Si$. The ^{13}Cnmr spectrum agreed with the required structure and all the resonances were assigned (see experimental). The mass spectrum has a molecular ion peak at m/e 254. Major fragamentation peaks were at m/e 197 (M-C(CH_3)$_3$), and m/e 105.

Attempts to synthesise the methyl enol ether of 3-oxabicyclo[3.3.1]nonan-6-one (165) were less successful. Reaction of 3-oxabicyclo[3.3.1]nonan-6-one (158) with 2,2-dimethoxypropane-PTSA-MeOH in DMF[162] gave mainly the acetal (164) with a small amount of the methyl enol ether (165). These could be separated by column chromatography. The

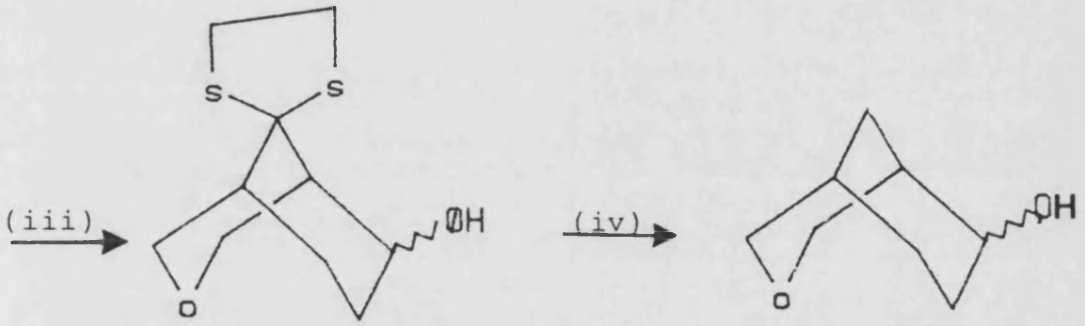
ketal (164) showed no carbonyl absorption in the i.r. spectrum. The ^{1}Hnmr spectrum showed the two methoxy groups of the acetal as singlets at δ3.19 and 3.15. The ^{13}Cnmr spectrum was in accord with this structure. The mass spectrum had a base peak at m/e 185(M^{-1}). Main fragmentations were losses of the methoxy groups at m/e 153 and m/e 123. The acetal was converted to the methyl enol ether (165) by refluxing with PTSA in trimethylortho formate.[163] The i.r. spectrum gave the required double bond stretch at 1640cm^{-1}. The ^{1}Hnmr spectrum showed a triplet at δ4.7 attributable to the resonance of H-7, and a singlet at δ3.45 for the methoxy group confirming the presence of the methyl enol ether. The mass spectrum gave a molecular ion at m/e 154.

4.10 Summary

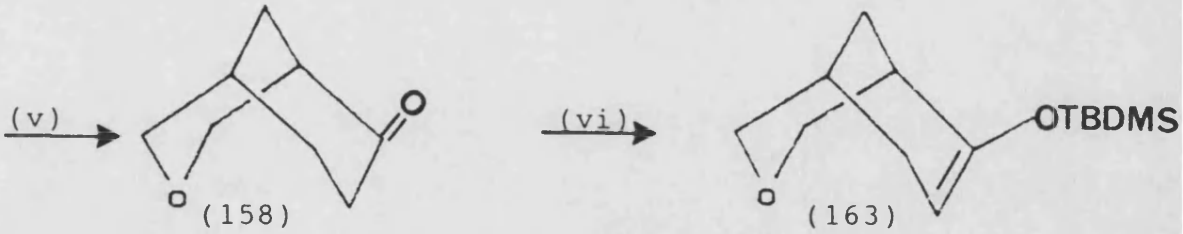
The idea behind the synthesis of the 3-oxabicyclo [3.3.1]nonanes was to use them as synthetic intermediates which could then be ozonylsed and further elaborated. Consequently high yielding reactions were required. The route chosen was that shown in Scheme 42. The TBDMS enol ether (163) was synthesised in an overall yield of 24% starting from tetrahydro-pyran-4-one (121). The TBDMS enol ether (163) had the advantages that once ozonylsed it would yield a bifunctional product and it could be obtained in higher overall yield than 3-oxabicyclo[3.3.1] non-6-ene (28).



(121) (122) (147) and (148)



(155) (156) and (157)



(158) (163)

Reagents:

(i) Pyrrolidine, benzene (ii) Acrolein,THF(aq)
(iii) Ethanedithiol,BF_3Et_2O,DCM
(iv) Raney Nickel, Absolute ethanol (v) PCC,DCM
(vi) TBDMs triflate, 2,6 lutidine,DCM

Scheme 42

4.11 ^{13}Cnmr of 3-oxabicyclo[3.3.1]nonanes

It has been shown that the ^{13}Cnmr chemical shifts are sensitive to stereochemical factors. Moreover, the effects of substituents on ^{13}C shieldings are often additive within a class of compounds.[164] These features make ^{13}Cnmr a powerful method for conformational analysis.

The conformational influences on ^{13}C chemical shifts for bicyclo[3.3.1]nonanes and 3-oxabicyclo[3.3.1]nonanes are reported to be about the same.[165] Apparently the steric effects of the ether oxygen atom on the chemical shifts are about the same as those of the CH_2 group. Empirical force field calculations[166] show that the tetra hydropyran ring in 3-oxabicyclo[3.3.1]nonane is much less flattened than the corresponding ring in the carbocyclic system. This explains the strong preference of 3-oxabicyclo [3.3.1]nonane for the C-C conformation.

It has been found that after correcting for substituent effects, the ^{13}C chemical shifts of bicyclo [3.3.1]nonane derivatives are characteristic for their conformation.[167] Consequently ^{13}Cnmr data is useful in estimating the conformational preferences of bicyclo[3.3.1] nonane derivatives.

The ^{13}C chemical shift data of various 3-oxabicyclo [3.3.1]nonanes are collected in Table 5. The assignments of the chemical shifts were based on standard methods, i.e. off resonance decoupling, and by comparison of chemical shifts between related compounds. Methylene, methine and methyl protons were assigned using the 135

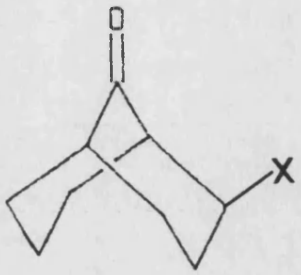
Table 5 ^{13}Cnmr chemical shifts (ppm) for 3-oxabicyclo[3.3.1]nonanes

Compound	C-1	C-2	C-4	C-5	C-6	C-7	C-8	C-9
3-oxabicyclo[3.3.1]nonane	30.0	73.4	73.4	30.0	31.2	22.5	31.2	33.3
Exo 6-hydroxy 3-oxabicyclo [3.3.1]nonan-9-one(147)	49.87	75.67	70.94	57.38	76.53	29.22	29.22	214.11
Endo 6-hydroxy 3-oxabicyclo [3.3.1]nonan-9-one(148)	48.46	74.48	68.70	57.41	74.96	30.44	27.25	212.65
Exo 6-chloro 3-oxabicyclo [3.3.1]nonan-9-one(150)	49.49	76.65	74.42	57.88	64.92	30.77	28.38	210.16
Endo 6-chloro 3-oxabicyclo [3.3.1]nonan-9-one(151)	49.44	76.69	71.33	56.87	61.90	31.53	27.73	210.12
Exo 6-hydroxy 3-oxabicyclo [3.3.1]nonane (156)	28.55	73.04	69.56	36.14	72.91	30.32	26.39	31.76
Endo 6-hydroxy 3-oxabicyclo [3.3.1]nonane (157)	29.34	73.38	66.48	36.33	70.58	30.91	25.33	31.14

and 90 Distortionless Enhancement by Polarisation transfer (DEPT) technique. This involves employing a θy pulse of 90°, when CH_2 and CH_3 carbons cancel and only CH's remain. When the pulse is 135° then CH's and CH_3's give a positive intensity whereas the CH_2's give a negative reading.

It is well known that the magnitude of substituent effects depend on the nature and the orientation of the functional group. Upon replacement of a functional group, the carbon bearing the functionality (the α carbon) and the carbon immediately adjacent to the carbon containing the substituent (the β carbon) usually experience downfield shifts. On the other hand, the carbons γ to the substituent usually exhibit upfield shifts. In the epimeric 2-substituted bicyclo[3.3.1]nonan-9-ones (Figure 19) it was shown that there was more pronounced deshielding of α-carbons in the exo isomers compared to the endo isomers.[168] It is unsure whether this effect was electronic in origin or was caused by slight differences in molecular geometry, since endo groupings may introduce steric interactions which could be partially relieved by some distortion of the carbon skeleton.

This type of effect is seen in the 6-substituted 3-oxabicyclo[3.3.1]nonanes with greater deshielding in the exo isomers (3.02-1.57 ppm). Considering the β-effect at the bridgehead carbons (C-5) only small differences are noticeable, while the βC-7 methylene carbons are shifted downfield in the case of the endo isomers. The



X=Exo-OH
Endo-OH
Exo-Cl
Endo-Cl
Exo-OTs
Endo-OTs

Figure 19

γ-effect is evident in carbon C-4 and this is used to differentiate between carbons 2 and 4 as carbon 4 has a shielding effect.

In order to reveal conformational preferences in the substituted 3-oxabicyclo[3.3.1]nonanes, it is primarily necessary to correct for substituent influences. As mentioned before substituent influences in bicyclo[3.3.1] nonanes are independent of ring conformation. Therefore, it is assumed that the same substituent effects can be applied for the 3-oxabicyclo[3.3.1]nonanes.

Table 6 Substituent effects in 2-substituted bicyclo [3.3.1] nonan-9-ones[a,b]

	α	β(C-5)	β(C-7)	γ(C-4)	γ(C-8)	γ(C-9)
Exo - OH	42.6	8.2	8.0	-3.6	-5.1	-1.6
Endo - OH	39.2	7.9	9.0	-7.0	-6.5	-2.4
Exo - Cl	31.3	8.1	7.9	-1.5	-4.3	-5.5
Endo - Cl	27.5	7.4	11.0	-5.4	-4.4	-5.9

a) Substituent effects are in ppm relative to bicyclo [3.3.1] nonan-9-one; a minus sign denotes a high field shift on substitution. b) Ref.168

Table 7 Substitution effect of 9-oxo function[a]

α	β	γ	δ
185.6	18.6	2.6	-2.0

a) Relative to bicyclo[3.3.1]nonane in ppm

It was anticipated that using the above substituent effects it would be possible to determine conformation preferences assuming that the parent 3-oxabicyclo[3.3.1] nonane is in the double chair conformation.

After correcting for the 6-substituent (only α, β and γ effects taken into account) and for the 9-oxo function (α, β, γ and δ effects), the chemical shifts of corresponding carbon atoms within the series agree closely and the values are shown in table 8. For

Table 8 ^{13}C Chemical shifts (ppm) of 3-oxabicyclo[3.3.1]nonanes (substituent corrected)

	C_1	C_2	C_4	C_5	C_6	C_7	C_8	C_9
3-oxabicyclo[3.3.1]nonane[165]	30.1	73.4	73.4	30.0	31.2	22.5	31.2	33.3
Exo 6-hydroxy 3-oxabicyclo [3.3.1] nonan-9-one(147)	31.2	73.1	72.0	30.5	30.5	23.2	31.7	30.1
Endo 6-hydroxy 3-oxabicyclo [3.3.1] nonan-9-one(148)	29.9	71.9	73.1	30.9	33.0	23.4	31.2	30.0
Exo 6-chloro 3-oxabicyclo [3.3.1] nonan-9-one(150)	30.8	74.0	73.3	31.1	31.6	24.7	31.3	31.0
Endo 6-chloro 3-oxabicyclo [3.3.1] nonan-9-one(151)	30.8	74.1	74.1	30.9	31.8	22.5	29.8	30.5
Exo 6-hydroxy 3-oxabicyclo [3.3.1]nonane (156)	28.6	73.0	73.1	28.0	30.3	22.3	31.5	33.4
Endo 6-hydroxy 3-oxabicyclo [3.3.1]nonane (157)	29.3	73.4	73.5	28.4	31.3	21.9	31.8	33.5

Table 9 ^{13}C chemical shifts (ppm) of the conformations of bicyclo[3.3.1]nonane[165]

CONFORMATION	^{13}C chemical shifts (ppm)								
Bicyclo[3.3.1]nonanes	C_1	C_2	C_3	C_4	C_5	C_6	C_7	C_8	C_9
cc	28.1	31.5	22.3	31.5	28.1	31.5	22.3	31.5	34.4
cb	25.9	33.3	16.4	33.3	25.9	26.7	19.0	26.7	28.6
bb	26.3	31.4	20.7	31.4	26.3	31.4	20.7	31.4	23.7

comparison the average ^{13}C for the various established conformations of the carbocyclic system are included for reference.[165] (table 9)

The ^{13}C chemical shifts clearly indicate that the various 3-oxabicyclo[3.3.1]nonane derivatives occur predominantly in the CC conformation. In particular the C_7 chemical shifts agree very well with those of the parent system. The C-7 chemical shift has often been used as a conformational probe and in our case the C-7 chemical shifts clearly indicate that they are in the CC conformation. Obviously, the shifts of the other carbon atoms are subject to the influence of the hetero-atom, but the conformational influences on their shifts observed in the carbocyclic compounds can still be recognized here.

5. Ozonolysis of silyl enol ethers and elaboration of side chains

5.1 Synthetic strategy

Ozonolysis has been widely used both in degradative work and in synthesis for the preparation of aldehydes, ketones and carboxylic acids. A way of achieving bifunctionality has been with the use of silyl enol ethers.[160] (figure 20)

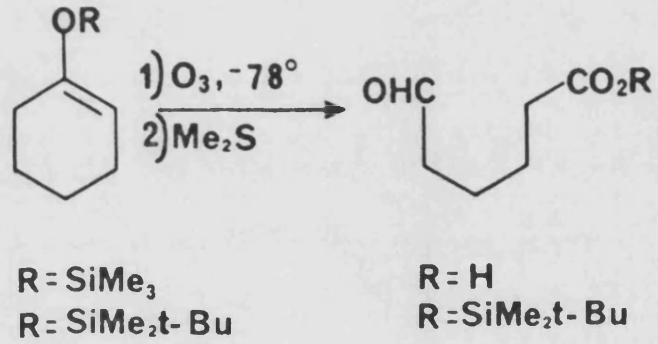
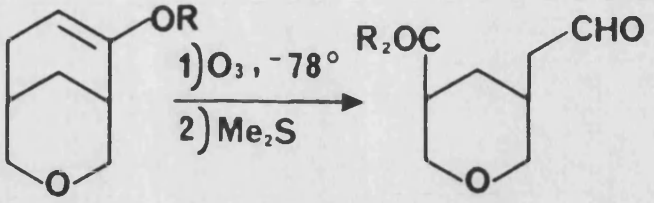


Figure 20

As can be seen from figure 20 the terminii are in different oxidation states and consequently it should be possible to perform selective reactions on either end. With this concept in mind we envisaged utilizing the silyl enol ethers of 3-oxabicyclo[3.3.1]nonan-6-one. It was anticipated that these would be ozonolysed and then selective Wittig reactions would be attempted.

5.2 Ozonolysis of silyl enol ethers of 3-oxabicyclo [3.3.1]nonan-6-one (158)

The trimethylsilyl enol ether (162) and t-butyldimethyl silyl enol ether (163) were ozonolysed as shown in Scheme 43.



(162) R = $SiMe_3$ (166) R = H
(163) R = $SiMe_2t$-Bu (167) R = $SiMe_2t$-Bu

Scheme 43

It was important to monitor the reaction closely. Normally in ozonolysis the reaction is complete when the blue coloration persists. However, this was not a sufficient criterion to show that the reaction had gone to completion. The reaction had been stopped when a blue colour had appeared and there was still starting material present. Starch-iodine paper was used to indicate the presence of excess oxidant. It was important to do this frequently, time depending on the size of reaction, as if it was left too long over-oxidation occurred. The trimethylsilyl enol ether (162) gave the desired aldehyde-carboxylic acid (166) in over 90% yield and this was purified by column chromatography (PE/EtOAC, 1:1 + 1% formic acid). The t-butyldimethylsily enol ether (163) gave the desired aldehyde-siloxy ester (167) in approximately 90% yield. However, all methods of purification of this compound failed. Distillation, chromatography using triethylamine-treated silica and

chromatography using neutral alumina failed to produce the desired compound. Spectral data were recorded on the crude compound and indicated relatively high purity (>90%). The ir spectrum showed a broad carbonyl stretch at 1700cm^{-1}. In the nmr spectrum there was a multiplet for the aldehydic proton at δ9.75. Multiplets were seen at δ4.15, 3.85, 3.36 and 2.95 for the methylene hydrogens adjacent to the ether oxygen and a multiplet at δ2.7 for the bridgehead hydrogen adjacent to the siloxy ester grouping. A multiplet was seen at δ2.35 for the other bridgehead hydrogen and the hydrogens nearest the aldehyde, and a multiplet at δ1.7 for the remaining ring hydrogens. The two singlets attributable to the resonances of the hydrogens of $(CH_3)_3CSi$ and $(CH_3)_2Si$ occur at δ0.95 and 0.15 respectively. The mass spectrum gave a molecular ion (C.I.) at m/e 285. The base peak was at m/e 127. Major fragmentations are shown in figure 21.

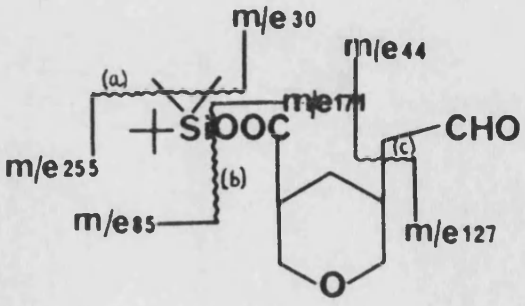
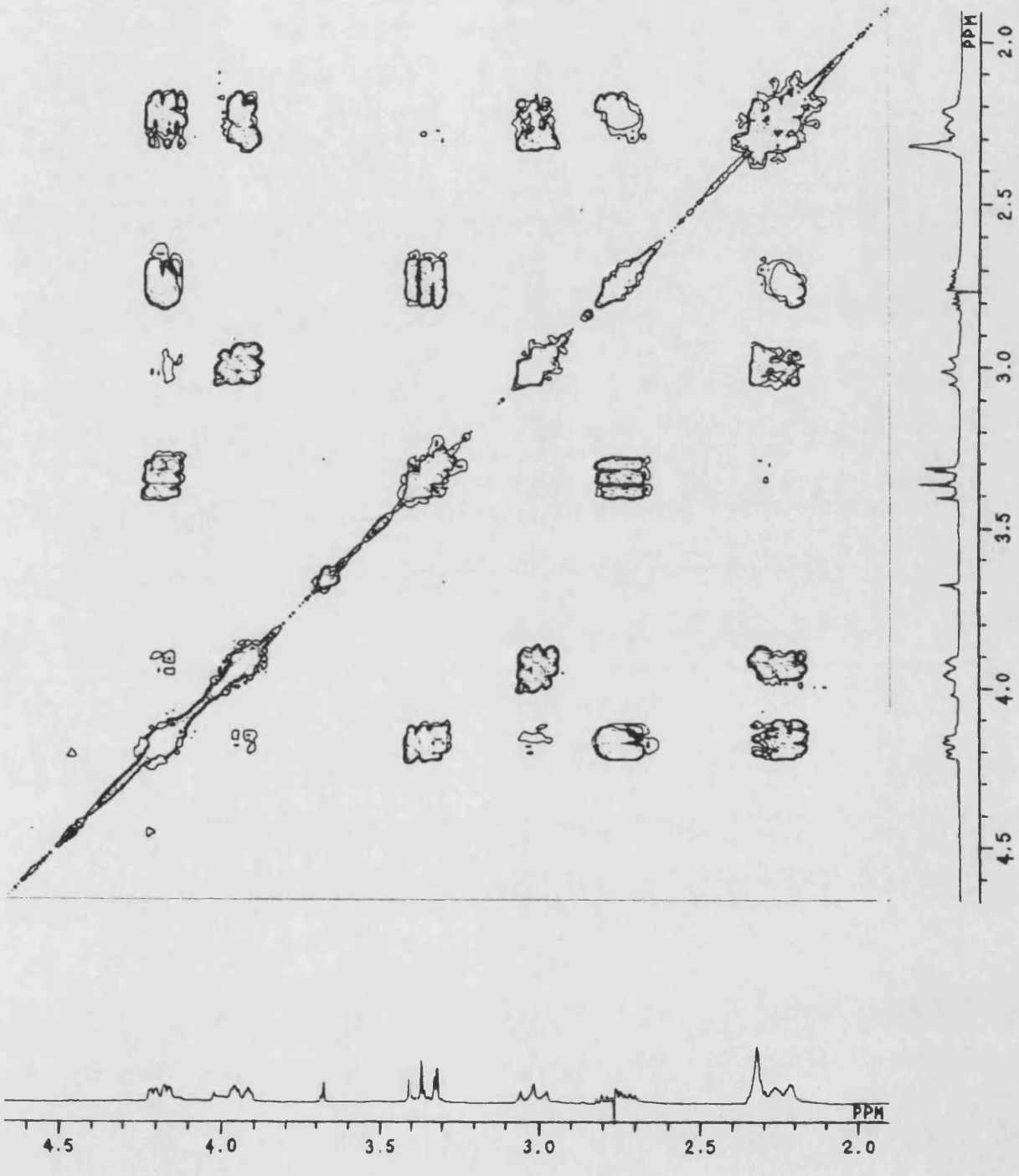


Figure 21

The difficulties encountered in purification led us to deprotect the siloxy ester (167) to give the carboxylic acid (166) (Scheme 44). This was achieved using a mixture of acetic acid, H_2O and THF (3:1:1)[132] and gave the desired compound in 81% yield. It is worth noting that tetra n-butylammonium fluoride in THF[132] gave none of the desired compound. 5-(2-formylmethyl)-3-tetrahydropyran carboxylic acid (166) was obtained as a white solid (m.p. 127-128°). The ir spectrum showed a carboxylic acid stretch (3500-3000cm^{-1}) and a carbonyl stretch at 1700cm^{-1}. The ^{1}Hnmr spectrum was assigned by decoupling experiments and by use of a COSY spectrum (page 130). The aldehydic proton was seen as a multiplet at δ9.9 and the carboxylic acid proton as a broad singlet at δ9.0. There are four resonances centred at δ4.19, 3.94, 3.35 and 3.05 attributable to C-2(Heq), C-4(Heq), C-2(Hax) and C-4(Hax) respectively, the protons of the methylenes adjacent to the ether oxygen. Multiplets were seen at δ2.75 for the bridgehead nearest the carboxylic acid and at δ2.35 for the other bridgehead proton. The methylene adjacent to the aldehyde appeared as a multiplet at δ2.31 and the methylene at C-6 appeared as a quartet at δ1.4. The COSY spectrum indicated retention of stereochemical integrity from the ozonolysis reaction as there was evidence of coupling between the two bridgehead hydrogens and therefore a cis arrangement.

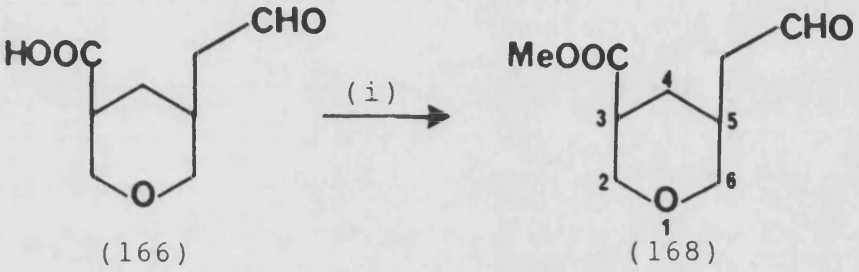
The mass spectrum gave a M^{-1} peak at m/e 171, which also corresponded to the base peak. The main fragmentation



COSY Spectrum of 5-(2-Formylmethyl)-3-tetrahydro-pyran carboxylic acid (166)

was at m/e 129 corresponding to the loss of the aldehyde side chain.

The aldehyde-carboxylic acid (166) was also converted into its methyl ester (168) using diazomethane[119] and was obtained in a quantitive yield.



(166) (168)

Reagents (i) CH_2N_2, Ether, 0°

Scheme 44

The ir spectrum showed one carbonyl band at 1720cm^{-1}. In the ^{1}Hnmr spectrum the aldehydic proton was seen as a multiplet at δ9.9. Multiplets were seen at δ4.14, 3.92, 3.33 and 3.01 for C-2Heq, C-4Heq, C-2Hax and C-4Hax respectively (the protons of the methylenes adjacent to the ether oxygen). The methyl ester appeared as a singlet at δ3.7. The two bridgehead protons, H_1 and H_5 were seen as multiplets at δ2.7 and 2.28 respectively. Multiplets were seen at δ2.16 for the methylene next to the aldehyde and at δ1.4 for the methylene at C-6. The mass spectrum gave a M^{-1} peak at m/e 185. The base peak was at m/e 143 corresponding to the loss of the aldehyde side chain, other major fragmentations are shown in figure 22.

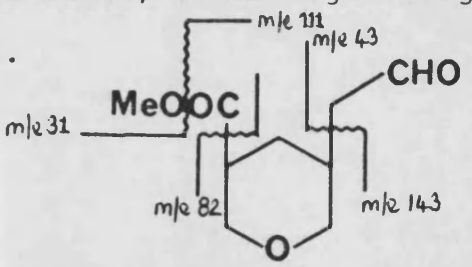
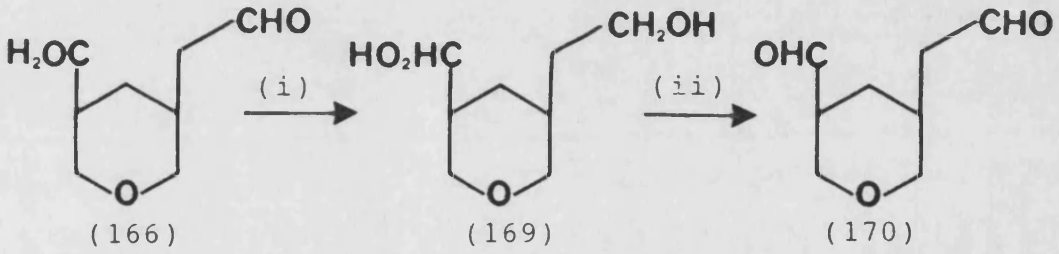


Figure 22

5.3 Synthesis of 5-(2-formylmethyl)-3-tetrahydropyran carbanal (170)

5-(2-formylmethyl)-3-tetrahydropyrancarbanal (170) was synthesised starting from the aldehyde-carboxylic acid (166), which was converted to the dialcohol (169) by diborane.[170] The ir spectrum showed the absence of the carboxylic acid and carbonyl stretches and gave a stretch for the hydroxyl group at 3650 and 3450cm^{-1}. The dialcohol (169) was then oxidised using pyridinium chlorochromate[156] to give the dialdehyde (170) in a yield of 57%.



(166) (169) (170)

Reagents: (i) Diborane, 0° (ii) PCC,DCM

Scheme 45

The structure of the dialdehyde was confirmed by the ir spectrum showing a carbonyl stretch at 1710cm^{-1} and the ^{1}Hnmr spectrum, where two multiplets were seen at δ9.85 and 9.65 corresponding to the two aldehydic protons.

5.4 The Wittig reaction

The Wittig reaction has proved to be synthetically a very useful reaction, involving the reaction of a phosphonium ylid with an aldehyde (or ketone) to give an olefin and phosphine oxide. An important aspect of this reaction has been the control of stereochemistry to give either cis or trans olefins. A phosphonium ylid and an aldehyde can react to give two diastereomeric betaines (171 and 172). The relative rates of formation and decomposition of these betaines control the stereochemistry of the olefin mixture produced by the Wittig reaction. The trans betaine is favoured thermodynamically, as being in the eclipsed form it has a minimum of steric interactions. However, the cis-betaine is the kinetic product (i.e. formed first). If formation of the betaine is the rate determining step, the betaine will decompose rapidly to the olefin and consequently give the cis-olefin. If however the rate of decomposition of the betaine becomes comparable to the rate of formation, then betaine reversibility becomes important, and the proportions of betaines present depends on their thermodynamic stability rather than their rate of formation, and so the proportion of trans-olefin increases. The factors affecting kinetic and thermodynamic control are listed in table 10.

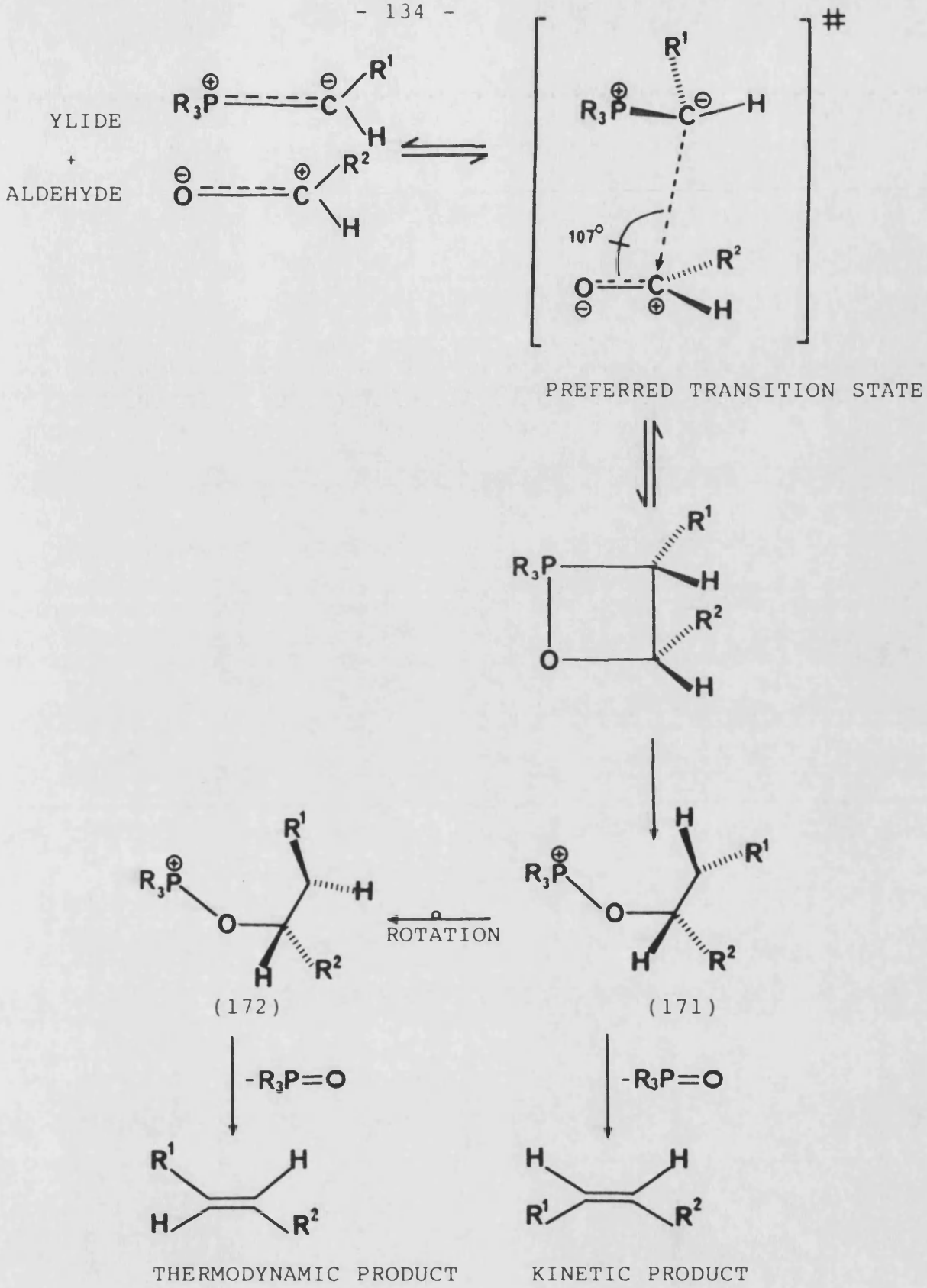


Figure 23 CONTROL OF CIS AND TRANS OLEFIN FORMATION

Kinetic control (cis)	Thermodynamic control (trans)
Low temperatures	Elevated temperatures
Polar, aprotic solvents	Apolar, protic solvents
Lewis base	Betaine stabilizing salts
Salt free solutions	Carbanion stabilization
No carbanion stabilization	R^1=CN, COOR, COR, Aryl,Vinyl
(R^1= alkyl, alkoxy)	Electron rich phosphorus atom
Electrophilic phosphorus atom	PR_3^+
PPh_3^+	Excess base

Table 10

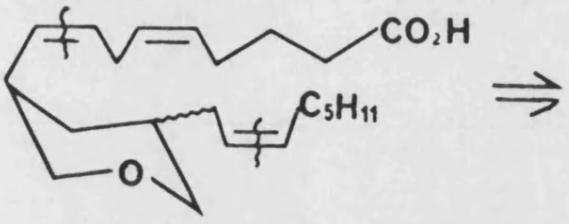
Therefore by choosing the correct conditions it should be possible to perform a stereospecific synthesis. In our case we wanted stereospecifically to produce the cis-olefin.

5.5 Wittig Reactions

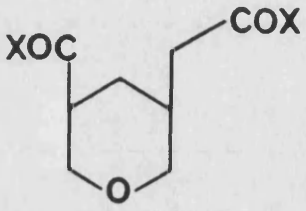
5.5.1 Introduction

Having successfully ozonolysed the 3-oxabicyclo [3.3.1]nonane ring system the next step was to perform selective Wittig reactions on the respective side chains (see Scheme 46).

The Wittig reagent (173) can be bought as can the methyl ester of (176). The Wittig reagent (174) has been synthesised by two groups[171,172] both involving eight step sequences. It was envisaged synthesising



(23)



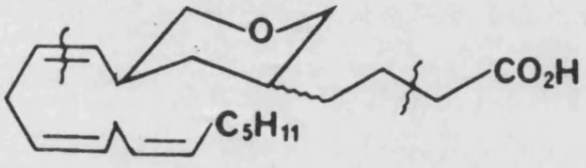
(27) X=H or OR

$+C_6H_{13}\overset{+}{P}Ph_3Br^-$

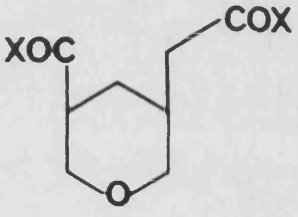
(173)

$+H_2OC(CH_2)_4C{=}CH(CH_2)_2\overset{+}{P}Ph_3Br^-$

(174)



(177)



(27)

$+C_5H_{11}CH{=}CHCH_2CH{=}CH(CH_2)_2\overset{+}{P}PhBr^-$

(175)

$+H_2OCCH_2\overset{+}{P}PhBr^-$

(176)

Scheme 46

the Wittig reagent (175) by our own route, which will be discussed at a later stage.

5.5.2 Attempted Wittig reactions on 5-(2-formylmethyl)-3-tetrahydropyranmethyl t-butyldimethylsiloxy carbonyl (167)

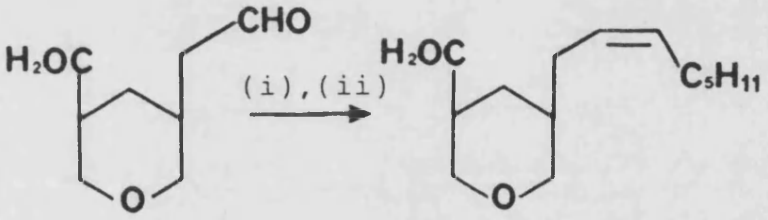
Originally it was anticipated performing the Wittig reactions on the aldehyde-siloxy ester. Unfortunately attempted Wittig reactions were unsuccessful. The conditions chosen were those of Corey et al,[23] who had used them in a synthesis of LTB_4. They involved the use of nBuLi as the base in THF, the important factor being the addition of 15 equivalents of HMPA (based on the phosphonium salt). These conditions were reported to give exclusively cis-olefins.

In the case of the aldehyde-siloxy ester none of the desired compound was obtained, although starting material disappeared. This may be due to lability of the siloxy-ester grouping, as it is known that the siloxy ester grouping reacts with nBuLi and that the original functionality (i.e. carboxylic acid) is not restored.[173] Consequently, any excess base present would have an adverse effect on the reaction. The lability of the siloxy-ester grouping led us to deprotect and attempt the Wittig rection on the free carboxylic acid.

5.5.3 Synthesis of 5-(cis-2-octenyl)-3-tetrahydropyran carboxylic acid (178)

It was decided, because of the failure of (167) to react with Wittig reagents, to use the aldehyde-

carboxylic acid (166). Obviously in this case we would have to use 2 equivalents of the phosphonium salt as one equivalent would be consumed by the carboxylic acid. The reaction of the aldehyde-carboxylic acid (166) with n-hexyltriphenylphosphonium bromide (173) gave the desired compound in a yield of 73%.



(166) (178)

Reagents: (i) BuLi,THF,-78°→ -20°→ -78°
(ii) HMPA(30eq),n-Hexyltriphenylphosphonium bromide(2eq)

Scheme 47

The ir spectrum indicated the presence of the carboxylic acid group (3500-3000cm^{-1}) and a carbonyl stretch at 1700cm^{-1}. The double bond was shown by the presence of =CH stretch at 3020cm^{-1}. The ^{1}Hnmr spectrum was in accord with the desired compound. The aldehydic peak had disappeared. The carboxylic acid proton was seen as a broad singlet at δ10.64. The resonances of the double bond protons were seen as multiplets centred at δ5.44 and 5.34. The resonances of the methylenes adjacent to the ether oxygen appeared as two multiplets

at δ4.15 and 3.93 and two triplets at 3.35 and 2.96. A multiplet was seen at δ2.66 for the methine nearest the carboxylic acid group. There were multiplets at δ2.2, 1.97, 1.69 and 1.26 and a triplet at δ0.88 (J=6.5Hz) for the terminal CH_3 group.

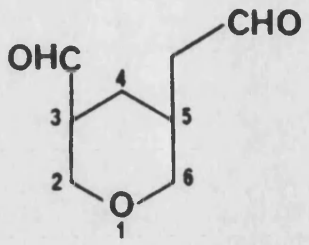
It was important to introduce the double bond in entirely the cis configuration and consequently we hoped that the conditions used would achieve the required stereochemical control of the Wittig reaction. By analogy from previous reactions where these conditions have been used we should obtain a purely cis-olefin. It is well known that the vicinal coupling for Jtrans is greater than Jcis. The value for Jtrans is 11-19Hz and Jcis is 5-14Hz. The vicinal coupling constant of (178) was calculated to be 10.99Hz and therefore the evidence points to (178) possessing a cis-olefin as we had anticipated.

The mass spectrum gave a molecular ion at m/e 240 and a base peak at m/e 141. This compound was sent for biological testing.

5.5.4 Attempted Wittig reaction on 5-(2-formylmethyl)-3-tetrahydropyrancarbanal (170)

It was hoped to be able to perform selective Wittig reactions on the dialdehyde (170) envisaging that the two aldehydes would be different in reactivity.

It was anticipated that the acetaldehyde group at C-5 would be more reactive due to its greater flexibility and therefore would react selectively. Unfortunately this was not the case, as there seemed



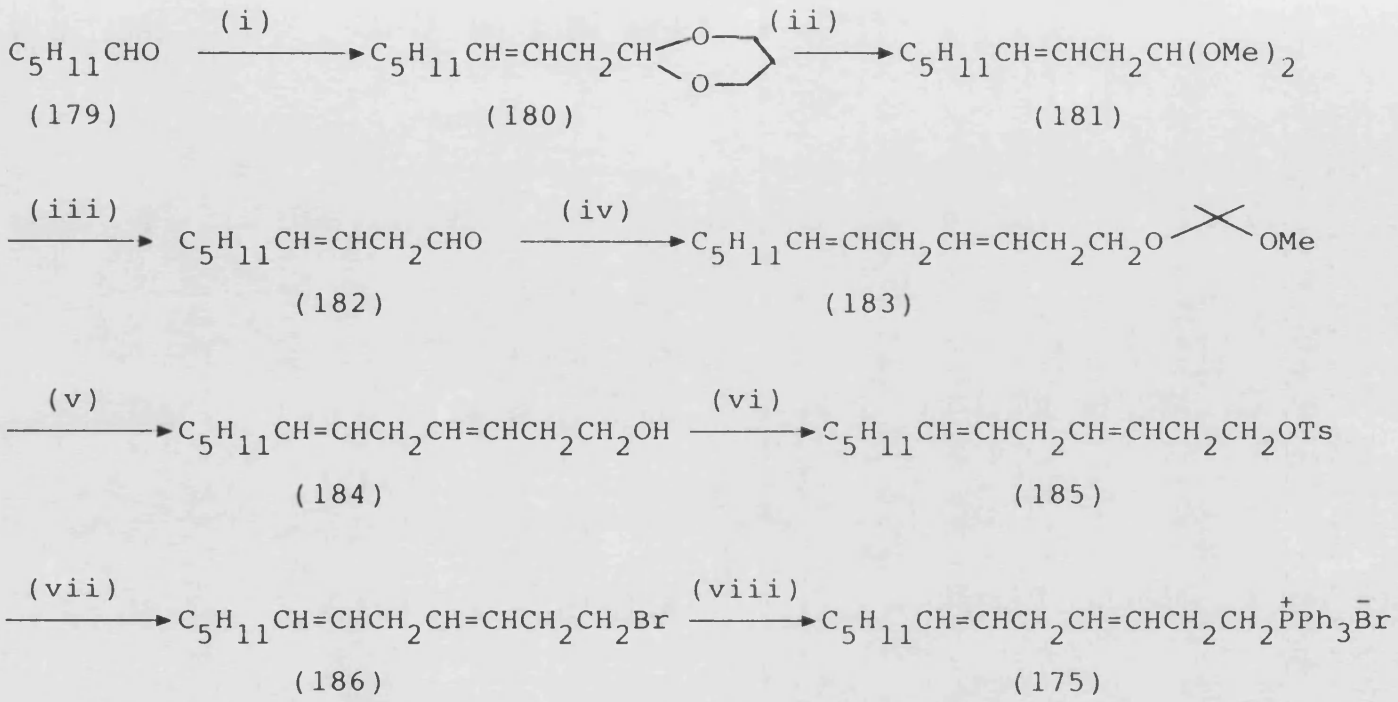
(170)

to be no appreciable difference between the two aldehydes. Using similar conditions that had been successful for the aldehyde-carboxylic acid (166) but only using one equivalent of the phosphonium salt and employing inverse addition in order to keep the concentration of the phosphonium salt low. Unfortunately a complex mixture was obtained.

5.6 Approach to the synthesis of Wittig reagent (175)

The starting point for the synthesis of (175) was from hexanal (179), and it was envisaged elaborating this to (175) by two three-carbon extensions (Scheme 48).

Hexanal (179) was reacted with the Wittig reagent, 2-(1,3-dioxan-2-yl)-ethylidenetriphenylphosphorane[174] to give 2-cis-(2-octenyl)-1,3-dioxane (180) in an 86% yield. The 1,3-propanediol was trans acetalised with acidic methanol as the six-membered ring acetal has a high equilibrium stability, such that simple acid



Reagents: (i) tBuOk, Hexane, 2-(1,3-Dioxan-2yl)-ethylidenetriphenyl phosphorane, RT, (ii) PTSA, MeOH, (iii) AcOH, H_2O

(iv) $MeO\times O(CH_2)_3\overset{+}{P}Ph_3Br^-$, -78° THF, nBuLi, HMPA

(v) THF/MeOH/H_2O 1:1:1 pH 4.0(HOAc), 0°

(vi) TsCl, Py, (vii) LiBr, Acetone (viii) Ph_3P, Benzene

Scheme 48

hydrolysis is unfavourable, to give (181). The dimethyl acetal (181) was then hydrolysed at room temperature in aqueous acetic acid to give the aldehyde (182). The ir spectrum showed a carbonyl stretch ($1730cm^{-1}$). The ^{1}Hnmr spectrum indicated the presence of the aldehyde, a triplet (J=2Hz) at δ9.65. The double bond appeared as two multiplets centred at δ5.68 and 5.56. It was assumed that we had the cis isomer by analogy with similar examples.[174] Unfortunately, it was at this point that the work had to be terminated.

5.7 Conclusion

From the work previously described it is clear that the work done has laid a firm foundation to the synthesis of a number of lipoxygenase inhibitors. The ozonylsis products of the TMS (162) and TBDMS (163) enol ethers are potentially versatile synthetic relay compounds for a large number of possible products and have laid the basis for future studies.

EXPERIMENTAL

INSTRUMENTATION AND EXPERIMENTAL TECHNIQUES

Infrared (ir) spectra were recorded in the range 4000-600cm^{-1} using Perkin Elmer 197 and 1310 grating spectrophotometers, with 0.05mm polystyrene film as a calibration reference (1601.4cm^{-1} absorption) and in the range 4000-400cm^{-1} using Perkin-Elmer 983 Fourier transform spectrophotometer. Peaks are separated in wave numbers. Spectra of liquid samples were taken as thin films, or as solutions in $CHCl_3$ or CH_2Cl_2. Spectra of solid samples were taken in $CHCl_3$ solution.

Routine mass spectra from both electron ionization (E.I.) and chemical ionization (C.I. reagent gas isobutane), and high resolution accurate mass determinations were recorded with a VG Analytical 7070E instrument with a VG2000 data system at an ionizing potential of 70eV where possible. The molecular ion peak (M^+) and base peak are indicated, as are all sizeable fragmentations.

Proton magnetic resonance (^{1}Hnmr) spectra were recorded at 60MHz on Hitachi Perkin-Elmer high resolution R24B and Varian Anaspect EM360 spectrometers, on Jeol 100MHz, 270MHz and 400MHz. ^{13}Cnmr spectra were determined with a Jeol FX90Q or GMNGXFT 270 spectrometer. ^{1}H and ^{13}Cnmr spectra were recorded, unless otherwise noted, in $CDCl_3$, and are expressed in parts per million (δ) downfield from internal tetramethylsilane. Multiplicities are given as follows: singlet (s), doublet (d), triplet (t), quartet (q), and multiplet (m).

Melting points (m.p.) were determined on commercially available apparatus (Gallenkamp) and are uncorrected. Elemental microanalyses were carried out using the Carlo Erba 1106 Elemental Analyser.

Thin layer chromatography (t.l.c.) was used extensively as a qualitative guide during reactions and for assessing purity of compounds. Art 5554 Merck DC-alufolien Kieselgel 60 F_{254} and Art 5550 Merck DC-alufolien aluminiumoxide 60 F_{254} neutral (Type E) sheets containing fluorescent indicator were used for this purpose. Visualisation of reaction components was achieved by illumination under short wavelength (254nm) ultraviolet light, and developing with a 7% (W/V) methanol solution of dodeca-molybdophosphoric acid (PMA) followed by warming the t.l.c. plate.

Medium pressure flash column chromatography was routinely employed using Kieselgel 60 and 60H silica gel (Merck) for reaction component separations. Pressure was applied using commercially available hand bellows (Gallenkamp). In most cases, columns were prepared in petroleum ether (60-80°) and eluted with ethyl acetate petroleum ether mixtures of steadily increasing polarity. Material to be chromatographed was pre-adsorbed onto the column support and applied as a thin layer to the top of the column.

Dry column "flash" chromatography was carried out as follows: such columns were packed in a sintered funnel, dry, and under suction of a water pump. They were pre-eluted with the least polar component of the

eluent. During this procedure, constant coverage of the stationary phase with this solvent was maintained, until collection of solvent in the receiver vessel was seen. The column was then allowed to be sucked dry. Sample mixture was loaded by either dissolving in a small amount of a suitable non polar solvent, preferably that used during pre-elution or by pre-adsorption. The column was sucked dry, and the mixture eluted using appropriate constant volumes of eluent, and the fraction in the receiver isolated.

In those cases where reduced pressure distillation was difficult, if not destructive of the heavier compounds, or when column chromatography was particularly difficult, very pure samples were obtained by employing preparative, centrifugally accelerated thin-layer chromatography (Model 7924 Chromatotron) 2mm absorbent layer (silica gel PF_{254} type 60 TLC from Merck) coated on circular plates was used for sample loadings of up to 300mg total sample.

Solvents were of SLR grade, unless otherwise stated. Where water was used, this had been glass distilled once. Anhydrous solvents had been distilled under dry nitrogen and were stored over activated molecular sieves. Other dry solvents were stirred with a drying agent under reflux prior to distillation, as follows: DMF (P_2O_5), benzene (LAH). Tetrahydrofuran (THF) was pre-dried over sodium wire, then refluxed over sodium benzophenoneketyl under dry nitrogen until anhydrous.

This was re-distilled immediately prior to use.

All other general reagents and solvents were purified when required using the methods described by Perrin et al,[118] and those in Vogel.[119]

Glassware used for reactions under anhydrous conditions was baked in an oven at 120° for ca 12 hours and allowed to cool in a dessicator over silica gel. Flasks and stirring bars were, however, additionally flame dried under dry nitrogen.

In all experiments, the excess solvent was evaporated with a Buchi rotary evaporator by using water aspirator reduced pressure. Residual traces of solvent were removed on a manifold connected to an oil pump.

All temperatures are recorded in °C.

4-hydroxycyclohexanone[121](101)

A stirred solution of 1,4 cyclohexanediol (29g, 0.25mol) dissolved in acetone (1250ml) was cooled in an ice bath. To this was added ice-cold, freshly prepared Jones Reagent (30mls, 0.95 equivalent) over a 50 minute period. Jones Reagent prepared as follows: to CrO_3 (26.7g) at ice-bath temperature, cH_2SO_4(23mls) was added slowly and allowed to cool. The resultant solution was made up to 100mls with water, added slowly with stirring. After addition of Jones Reagent, the green suspension was allowed to warm to room temperature, with stirring over a 20 minute period. The chromium salts were allowed to settle and the acetone solution was decanted and twice suction filtered through a bed of celite. Acetone was removed on the rotary evaporator to yield a light green oil (containing approx. 20% of diketone). Columned using dry column "flash" chromatography with chloroform as elutant gradually increasing methanol content from 0-5%. This yielded a colourless oil (15.6g, 54%); ν_{max} (thin film) 3380(-OH), 1690cm^{-1} (C=O); $\delta_H(CDCl_3)$ 4.08 (m, 1H, C<u>H</u>OH), 3.62 (br.s, 1H, CHO<u>H</u>), 2.82-1.76 (m, 8H; ring); δ_C 212.15 (s, C-1), 65.82 (d, C-4), 37.17 (t, C-2, C-6), 33.64 (t, C-3, C-5); <u>M/Z</u> (70ev E.I.); 114 (M^+, 100%), 73, 68, 60, 55, 54, 41, 39.

8-hydroxy-1,4-dioxaspiro[4.5]decane[121](102)

To a magnetically stirred solution of crude (101) (27g, 0.24mol) in benzene (550mls) was added ethane-1,2-

diol (14.9g, 0.24mol). The flask was equipped with a Dean and Stark water separation apparatus and the reaction mixture was refluxed for 14-22 hours until no more water separated. The cooled reaction mixture was washed with saturated $KHCO_3$ (1 x 30ml) and the benzene layer separated and dried ($MgSO_4$). Benzene was evaporated to yield a pale yellow oil (21.6g, 57%), which was used without further purification. ν_{max} (thin film) 3400 (-OH), 1100 and 1030cm^{-1} (C-O-C); $\delta_H(CDCl_3)$ 4.08 (1H, br.m, CHOH), 3.9 (s, 4H, $OC\underline{H}_2C\underline{H}_2O$), 3.6 (br.m, 1H, $CHO\underline{H}$), 2.0-1.7 (m, 8H, ring).

8-(2-propenyloxy) 1,4-dioxaspiro[4.5]decane (103)

A magnetically stirred slurry of sodium hydride (2.2g, 0.09) in dry DMF (100mls) was prepared as follows: sodium hydride, stabilised in mineral oil (3.7g) was added to a flame dried flask, which was stoppered with a septum and flushed with dry N_2. The mineral oil was next removed by washing with pentane (3 x 20mls) when the pentane had evaporated, the DMF was added. To this stirred slurry was added (102) (12.7g, 0.08mol), dissolved in dry DMF (10mls), dropwise. After evolution of gas had ceased, dry potassium iodide (10g) was added followed by the dropwise addition of allyl bromide (freshly distilled) (13.9g, 0.12mol) dissolved in dry DMF (10mls). The reaction mixture was then stirred at room temperature for 10-15 hours. The mixture was then poured into water (500mls) and sodium chloride (50g) added. The mixture

was extracted with ether (3 x 200mls) and dried ($MgSO_4$). Removal of the solvent yielded a yellow oil (11.1g). This was purified by dry column "flash" chromatography (PE/EA, 5:1) to yield a colourless oil (10.6g, 67%) Found: C,66.5; H,9.4 calc. for $C_{11}H_{18}O_3$; C,66.7; H,9.1%; ν_{max} (thin film) 1640vw (C=C), 1100 and 1030cm^{-1} (C-O-C); $\delta_H(CDCl_3)$ 6.16-5.74 (m, 1H, $J_{2',-3'}$, trans = 17Hz, $J_{2',-3'}$, cis = 10Hz, $J_{2',-1'}$ = 5Hz, $C\underline{H} = CH_2$), 5.40-5.04 (t, 2H, $CH = C\underline{H}_2$), 4.01 (s, 2H, $OC\underline{H}_2CH$), 3.92 (s, 4H, $OC\underline{H}_2C\underline{H}_2O$), 3.46 (br.m, 1H, $C\underline{H}O$), 2.00-1.40 (m, 8H, ring). $\delta_C(CDCl_3)$ 135.65 (d, C-2'), 116.04 (t, C-3'), 108.51 (s, C-4), 74.16 (d, C-8), 68.96 (t, C-1'), 64.25 (t, C-2, C-3) 31.42 (t, C-6, C-10), 28.66 (t, C-7, C-9); M/Z (C.I. iBuH) 199 (M^{+1}, 100%), 141, 69, (70ev E.I.) 99, 86 (100%), 41.

8-(2-hydroxyethoxy) 1,4-dioxaspiro[4,5]decane[122](104)

A magnetically stirred solution of (103) (7.7g, 0.039mol), dissolved in chloroform (75ml) was cooled to -72°C (IMS/CO_2 bath). Ozone was passed through the solution until the latter changed colour, from clear to pale blue, whereupon the solution was degassed with nitrogen and allowed to warm up to room temperature. After a reflux condenser and a thermometer had been fitted to the reaction flask, a solution of sodium borohydride (11.8g, 0.31mol) in aqueous ethanol (50% V/V; 75mls) was slowly added to the stirred ozonide. The solution throughout was maintained at room temperature. Then

the reaction mixture was warmed on a water bath (50°C) for 2½ hours with continued stirring, before being left to stand, unstirred for 10-15 hours. The mixture was neutralised with H_2SO_4 (10% w/v), the chloroform layer separated, and the aqueous layer further extracted with chloroform (3 x 75ml). The extracts were combined and dried ($MgSO_4$) and solvent was removed to yield a pale yellow oil (7.1g, 93%). T.L.C. (EtOAC) indicated that this was pure enough for next stage. However, a small sample was columned ("flash" chromatography) for analysis purposes; Found: C,59.38; H,8.99, calc. for $C_{10}H_{18}O_4$: C,59.41; H,8.91%; ν_{max} (thin film) 3460 (-OH), 1095, and 1030cm^{-1} (O-C-O); $\delta_H(CDCl_3)$ 3.93 (s, 4H, $OC\underline{H}_2C\underline{H}_2O$), 3.56 (m, 5H, $C\underline{H}OC\underline{H}_2C\underline{H}_2$), 2.46 (br.s, 1H, $O\underline{H}$), 1.76 (m, 8H, ring); $\delta_C(CDCl_3)$ 108.46 (s, C-5), 75.25 (d, C-8), 69.45 (t, C-1'), 64.20 (t, C-2, C-3), 61.81 (t, C-2'), 31.37 (t, C-6, C-10), 28.55 (t, C-7, C-9).

4-(2-hydroxyethoxy)-cyclohexanone (105)

Method A:

A solution of (104) (1.1g, 5.5mmol) dissolved in aqueous acetic acid (AcOH:H_2O 3:1 v/v; 30ml) was stirred magnetically for 18 hours at room temperature. The reaction mixture was then neutralised with aqueous sodium hydroxide (4M) before being extracted with ethyl acetate (2 x 30ml) and dried ($MgSO_4$). Removal of solvent afforded a yellow oil (0.74g). This was vacuum distilled on a Kugelrohr (150°C/0.1mm), yielding a colourless oil (0.54g,

66%).

Method B:

To a magnetically stirred solution of (104) (1.1g, 5.5mmol) dissolved in methanol (10mls) at room temperature was added perchloric acid solution (10%; 0.4ml). The solution was left to stir for 1½ hours, after which it was neutralised with sat. $NaHCO_3$(aq) and freed of methanol on a rotary evaporator. The residue was extracted with DCM (3 x 20mls), the combined extracts were dried ($MgSO_4$). Removal of the solvent afforded a pale yellow oil (0.79g). Vacuum distillation as in method A yielded a colourless oil (0.61g, 70%); Found: C,60.6; H,9.0; calc. for $C_8H_{14}O_3$; C,60.74, H,8.92%, ν_{max} (thin film), 3455 (-OH), 1710cm^{-1} (C=O); $\delta_H(CDCl_3)$ 3.68 (m, 5H, C<u>H</u>OC<u>H</u>$_2$C<u>H</u>$_2$OH), 2.78-1.55 (m, 9H, O<u>H</u>; ring); $\delta_C(CDCl_3)$ 211.50 (s, C-1), 73.30 (d, C-4), 69.78 (t, C-1'), 61.92 (t, C-2'), 37.11 (t, C-2, C-6), 30.50 (t, C-3, C-5); <u>M/Z</u> (C.I., iBuH) 159 (M^{+1}), 97 (100), 29.

<u>4-(2-tosyloxyethoxy) cyclohexanone (106)</u>

2g, (13mmol) of (105) in anhydrous pyridine (5ml) was added to p-toluenesulphonylchloride (2.56g, 13mol) in anhydrous pyridine (12ml). The solution was left stirring for 24 hours at 0° . Then H_2O(1ml) was added and stirring continued for 30 minutes. The reaction mixture was diluted with ether (100ml) and the solution was washed with H_2O, dil H_2SO_4(aq) and $NaHCO_3$(aq) and dried ($MgSO_4$). Removal of solvent gave a viscous yellow

oil (3.64g, 95%), which solidified on standing for two weeks. ν_{max} (thin film) 1355, 1170, 940cm^{-1}-sulphonate group. $\delta_H(CDCl_3)$ 7.4 (q, 4H aromatics), 4.15 (m, 2H, $C\underline{H}_2OTs$), 3.5 (m, 3H, $C\underline{H}OC\underline{H}_2CH_2OTs$), 2.1-1.3 (m, 8H, aliphatic ring).

8-(2-tosyloxyethoxy)-1,4-dioxaspiro[4.5]decane (107)

The ketal alcohol (104) (5.3g, 26mmol), dissolved in anhydrous pyridine (10mls), was added to a solution in anhydrous pyridine (25mls) of p-toluenesulphonylchloride (5.0g, 26mmol) which was magnetically stirred in a temperature controlled IMS bath (0°) for 24 hours. The reaction mixture was diluted with ether (50ml), washed with saturated $CuSO_4$(aq) (3 x 100ml), water (2 x 100ml), dried (Na_2SO_4) and evaporated to yield a yellow oil (7.4g, 91%) which was used for the next stage without further purification. ν_{max} (thin film) 1350, 1170 and 920cm^{-1} (SO_3); $\delta_H(CDCl_3)$ 7.4 (q, 4H, aromatics), 4.1 (m, 2H, $C\underline{H}_2OTs$), 3.9 (s, 4H, $OC\underline{H}_2C\underline{H}_2O$), 3.5 (m, 3H, $C\underline{H}OC\underline{H}_2CH_2OTs$), 1.85-1.0 (m, 8H, aliphatic ring).

4-(2-bromoethoxy)-cyclohexanone (108)[123]

A magnetically stirred solution of (107) (2.4g, 6.7mmol) and LiBr (11.4g, 0.13mol) dissolved in Analar acetone (40mls) was refluxed for 48 hours. The cooled suspension was concentrated down on a rotary evaporator, diluted with ether (50mls), washed with water (50mls) and dried ($MgSO_4$). Removal of solvent afforded a yellow

oil (1.6g). This was purified by chromatography (medium pressure) to yield a colourless oil (0.98g, 66%); Found: C,43.1; H,5.8 calc. for $C_8H_{13}BrO_2$: C,43.4, H,5.9; $\nu_{max}(CHCl_3)$, 1710cm^{-1} (C=O); $\delta_H(CDCl_3)$ 3.84, (m, 3H, C<u>H</u>O-C<u>H</u>$_2$) 3.52 (t, 2H, J ∿6Hz, C<u>H</u>$_2$Br), 2.82-1.64 (m, 8H, ring); $\delta_C(CDCl_3)$ 210.68 (s, C-1), 73.14 (d, C-4), 68.42 (t, C-1'), 37.00 (t, C-2'), 30.99 (t, C-2 C-6), 30.45 (t, C-3, C-5); M/z (low ev E.I.) 220/2 (M^+, 39%), 141 (100, M-Br), 113.

<u>4-(2-mesyloxyethoxy)-cyclohexanone (109)</u>

In a flame-dried flask continuously purged with dry nitrogen, a solution of (105) (175mg, 1.1mmol) and DMAP (220mg, 2.2mmol) dissolved in dry DCM (10ml) was magnetically stirred. Methanesulphonyl chloride (320mg, 2.8mmol) was added, followed by pyridine (440mg, 5.5mmol), whereupon the solution became cloudy. The reaction mixture was stirred for 2 hours before being diluted with DCM, washed with ice cold dil HCl (0.1M, 2 x 15ml) and ice cold H_2O (2 x 15ml), and dried ($MgSO_4$). Removal of solvent afforded a pale yellow oil (280mg), which was purified by "flash" chromatography (PE/EA 1:1). This yielded a colourless oil (234mg, 90%); $\delta_H(CDCl_3)$ 4.37 (br.m, 2H, C<u>H</u>$_2$OMs), 3.78 (m, 3H, C<u>H</u>OC<u>H</u>$_2$CH$_2$OMs), 3.04 (s, 3H, CH_3), 2.76-1.70 (m, 8H, ring). $\delta_C(CDCl_3)$ 210.41 (s, C-1), 73.62 (d, C-4), 69.34 (t, C-1'), 66.26 (t, C-2'), 37.54 (q, OMs), 36.95 (t, C-2, C-6), 30.34 (t, C-3, C-5); M/Z (70ev E.I.) 236 (M^+, 4%), 159, 141, 123, 96, 79, 68, 54, 41.

Reaction of 4-(2-tosylethoxy) cyclohexanone (106) with $KOBu^t$ in THF[120]

Using flame dried equipment in an atmosphere of dry N_2, a slurry of $KOBu^t$ (0.58g, 0.6mmol) was prepared in dry THF (10ml). To this was added slowly a solution of (106) (150mg, 0.5mmol) in THF (2ml). The mixture was stirred at 43-45° for 22 hours. The reaction was filtered, 10ml H_2O added to the filtrate and the solvent removed. The residue was extracted several times with pentane, the extracts washed with sat. Na_2SO_4(aq) and dried ($MgSO_4$). The solvent was then removed to yield 40mg of an oil containing 4-(2-hydroxyethoxy)-cyclohexanone (105) and other unidentifiable products.

Reaction of 4-(2-tosylethoxy) cyclohexanone (106) with LDA

(106) (0.25g, 0.85mmol) in dry THF (2ml) was added dropwise to a solution of LDA (1.1eq) at -78°C in an N_2 atm. The reaction mixture was stirred for ½ hr and then allowed to warm to room temperature. Quenched with NH_4Cl(aq) (5ml) and freed of THF. The residue was dissolved in ethyl acetate, washed with water, brine, dried ($MgSO_4$) and solvent evaporated to yield 90mg of a yellow oil of mainly starting material.

Reaction of 4-(2-tosylethoxy) cyclohexanone (106) with NaH in DME

To a stirred suspension under N_2 at room temperature of NaH (40mg, 1.7mmol), freed from mineral oil by washing with pentane (3 x 10ml) in dry dimethoxyethane (10ml)

was added dropwise over a period of 20 minutes a solution of (106) (200mg, 0.55mmol) in DME (5ml). The resulting mixture was heated under reflux for 20 hours. Upon cooling excess NaH was destroyed with ethanol, the reaction mixture was poured into H_2O (50ml), and extracted with ether (3 x 30ml). Combined ether extracts washed with H_2O, brine, dried ($MgSO_4$) and freed of solvent to give 30mg of an orange oil, which contained no identifiable product.

Reaction of 4-(2-tosylethoxy) cyclohexanone (106) with $KOBu^t$ in Bu^tOH

To a stirred solution at room temperature in a N_2 atmosphere, (106) (250mg, 0.8mmol) in dry t-butyl-alcohol (10ml) was added dropwise over a period of 5 minutes to a solution of $KOBu^t$ (93mg, 0.83mmol) in dry t-butylalcohol (5ml). The resulting mixture was refluxed for 2½ hours, cooled and poured into sat. brine (30ml). The organic material was extracted with ether (3 x 20ml), washed with brine, dried ($MgSO_4$) and solvent removed to yield 60mg of an orange oil. No identifiable product.

Reaction of 4-(2-bromoethoxyl)-cyclohexanone (108) with LDA

A solution of (108) (100mg, 0.45mmol) dissolved in dry THF (2ml) was added dropwise to a solution of LDA (1.1eq) at -78°C. The reaction mixture was left to stir for an hour at -78°C and was then allowed to warm to room temperature and left stirring overnight. Reaction quenched with NH_4Cl(aq) (2ml) followed by the

removal of THF. The residue was taken up in ether (20ml) washed with water (5ml), brine (2 x 5ml) and dried (Na_2SO_4). Removal of solvent afforded a yellow oil (80mg), which was found to be mainly starting material.

Reaction of 4-(2-bromoethoxy)-cyclohexanone (108) with $KOBu^t$

In a flame dried flask continuously purged with dry N_2 and fitted with a reflux condenser, ^tBuOK (115mg, 1mmol) in dry benzene (10ml) was stirred magnetically. A solution of (108) (150mg, 0.7mmol) in dry benzene (2ml) was added dropwise, leading to a change of colour of the reaction mixture, from clear to pale yellow. The stirred solution was refluxed for 2hours after which TLC (PE/EA 5:1) indicated the absence of any starting material. The reaction mixture was washed with brine (5ml) and dried (Na_2SO_4). Removal of solvent afforded a yellow oil (60mg), which was found to be a complex mixture containing starting material.

Reaction of 4-(2-mesyloxyethoxy)-cyclohexanone (109) with $KOBu^t$

In a flame dried flask continuously purged with dry N_2 and fitted with a reflux condenser, ^tBuOK (90mg, 0.8mmol) and dry THF (10ml) was stirred magnetically. A solution of (109) (100mg, 0.4mmol) in dry THF (2ml) was added dropwise. The solution remained clear for several seconds, then rapidly became yellow. The reaction mixture was refluxed for 10-15 hours. TLC (EA) indicated

no remaining starting material. The reaction mixture was freed of THF and taken up in ether (20ml), washed with H_2O (20ml) and dried (Na_2SO_4). Removal of solvent afforded a pale yellow solid (14mg), for which TLC indicated several components. Small scale column chromatography (PE/EA 5:1) largely succeeded in the separation of these. However, no identifiable material was isolated.

4-(chloroacetyloxy)-cyclohexanone (110)[127]

A solution of (101) (3.7g, 33mmol) dissolved in sodium dried ether (75ml) was stirred magnetically and pyridine (2.9ml, 36mmol) was added, followed by chloroacetylchloride (3.1ml, 39mmol) dropwise. The solution became cloudy on addition of chloroacetylchloride, then yellow shortly afterwards. The reaction mixture was left to stir for 4 hours. TLC (EA) indicated no starting material. The reaction mixture was washed with dil. HCl (0.1M, 2 x 25ml) and brine (2 x 25ml) and dried ($MgSO_4$). Removal of solvent afforded a yellow solid (5.6g) which was purified by flash chromatography (PE/EA, 5:1). This yielded a white crystalline solid, 4.9g, 77%); mp. 58-60°; Found: C, 50.10, H,5.79. $C_8H_{11}O_3Cl$ requires: C,50.39; H,5.77%; $\nu_{max}(CHCl_3)$ 1705cm^{-1} (C=O); $\delta_H(CDCl_3)$ 5.22 (m, 1H, C<u>H</u>) 4.10 (s, 2H, C<u>H</u>$_2$Cl), 2.76-1.90 (m, 8H, ring). $\delta_C(CDCl_3)$ 209.22 (s, C-1), 166.48 (s, C-1'), 70.48 (d, C-4), 40.85 (t, C-2') 36.73 (t, C-2, C-6), 29.90 (t, C-3, C-5); <u>M/Z</u> (C.I. iBuH) 191/3 (M^{+1}, 21%), 157, 97 (100).

Reaction of 4-(chloroacetyloxy)-cyclohexanone (110) with LDA

A solution of (110) (770mg, 4mmol) in dry THF (5ml) was added dropwise to a solution of LDA (1.1eq) in an N_2 atmosphere. The solution was stirred for 1 hour and then allowed to warm to room temperature. Reaction quenched with sat. NH_4Cl(aq), evaporated, dissolved in ethyl acetate, washed with H_2O, brine, dried (Na_2SO_4) and evaporated to yield 310mg of a brown oil, which consisted of a complex mixture of which no useful data could be extracted.

Reaction of 4-(chloroacetyloxy)-cyclohexanone (110) with NaH

Sodium hydride (60% suspension in mineral oil) (270mg, 12mmol) was washed three times with pentane (5ml). Dry DMF (4ml) was added to make a suspension. The reaction was conducted in an inert atmosphere (N_2). (110) (200mg, 11mmol) was dissolved in DMF (1ml) and added dropwise to the suspension. The reaction was stirred at room temperature and followed by TLC. Complex mixture obtained.

Reaction of 4-(chloroacetyloxy)-cyclohexanone (110) with DBU

(110) (100mg, 0.53mmol) was dissolved in dry DCM (5ml) in an atmosphere of dry N_2. DBU (0.16ml, 0.0106mol) was added dropwise and then stirred for 1 hour. Directly columned (silica) using ether as the elutant to yield

∿50mg of a colourless oil, which was 4-hydroxycyclohexanone (101).

Reaction of 4-(chloroacetyloxy)-cyclohexanone (110) with pyridine

(110) (100mg, 0.53mmol) was dissolved in dry pyridine (2ml) and refluxed for 1 hour. It was then partitioned between ethyl acetate and dil. HCl, washed with brine, dried and evaporated to yield ∿20mg of a pale yellow oil, which was found to be 4-hydroxycyclohexanone (101).

Reaction of 4-(chloroacetyloxy)-cyclohexanone (110) with KO^tBu

In a flame dried flask continuously purged with dry N_2 and fitted with a reflux condenser, KO^tBu (496mg, 4.42mmol) in anhydrous THF (50ml) was stirred magnetically. To this was added a solution of (110) (765mg, 4.02mmol). The stirred solution was refluxed for 2 hours after which the reaction was quenched with H_2O (5ml). The reaction mixture was freed of THF and taken up in Et_2O (30ml), washed with H_2O, brine and dried (Na_2SO_4). Removal of ether gave a viscous, deep orange-red oil (450mg). T.L.C. (PE/EA, 5:1) indicated seven components. These were separated using gradient elution "flash" chromatography (PE/EA from 5:1 to 1:1), producing six yellow oils and a pale yellow solid, which was shown to be starting material. Component 1, (first off column) 43mg, unidentifiable. Component 2, 57mg, starting material,

Component 3, 29mg, unidentifiable. Component 4, 23mg 2-oxabicyclo[3.3.1]non-3,6 dione (111), $\nu_{max}(CHCl_3)$ 1740, 1710 (C=O), 1280 (C-O-C); $\delta_H(CDCl_3)$ 5.15 (m, 1H), 2.6-1.8 (m, 9H). M/Z (70ev, E.I.) 154(M^+), 109 ($M-CO_2$), 97 (100), 96, 83, 80, 69, 57, 41. Component 5, 120mg unidentifiable. Component 6, 35mg 4-hydroxycyclohexanone (mainly). Component 7, 15mg $\nu_{max}(CHCl_3)$ 3520(-OH), 3150 (acid-OH), 2240, 1710 (C=O), 1420, 1280cm^{-1}, $\delta_H(CDCl_3)$ 5.1 (m, 1H), 3.4 (br.s, 1H, -OH), 2.6-1.8 (m, 10H). M/Z (70 ev. E.I.) 172 (M^+), 115, 97 (100), 96, 83, 69, 55, 41.

4-tertbutyldimethylsiloxycyclohexanone (116)[128]

A solution of (101) (3.37g, 0.03mol), t-butyldimethylchlorosilane (5.47g, 0.036mol) and imidazole (5.1g, 0.075mol) in dry DMF (10ml) was stirred for 48 hours at room temperature under a silica gel drying tube. The mixture was then poured into H_2O and extracted several times with ether. The ether extracts were back extracted with H_2O, dried (Na_2SO_4), and evaporated to yield 6.6g (96%), columned using dry column "flash" chromatography: PE/EA 10:1 to yield 6.15g (90%) ν_{max} (thin film); 1710 (C=O), 1260, 1110, 1050cm^{-1}; $\delta_H(CDCl_3)$ 4.15 (q, 1H, CHOTBDMS), 3.0-1.7 (m, 8H), 0.95 (S, 9H, Si-C(CH_3)$_3$, 0.15 (s, 6H, Si-(CH_3)$_2$; $\delta_C(CDCl_3)$ 216.26 (s, C-1), 70.86 (d, C-4), 41.77 (t, C-2, C-6), 39.06 (t, C-3, C-5), 30.66 (q, $(CH_3)_3$), 22.92 (s, C(CH_3)$_3$), -4.6 (q, Si-(CH_3)$_2$); M/Z (C.I. iBuH) 229 (M^{+1}), 171, 97.

2-t-butyldimethylsiloxyethylchloride

A solution of 2-chloroethanol (5g, 0.062mol), t-butyldimethylchlorosilane (9.35g, 0.074mol) and imidazole (10.57g, 0.16mol) in dry DMF (15ml) was stirred for 48 hours at room temperature under a silica gel drying tube. The mixture was then poured into water and extracted several times with ether. The ether extracts were back extracted with H_2O, dried (Na_2SO_4), and evaporated to yield a pale yellow oil, which was columned using dry column "flash" chromatography (PE/EA, 5:1) to yield 10.46g (87%) of a colourless oil. $\delta_H(CDCl_3)$ 3.88 (t, 1H, J, = 7Hz, $C\underline{H}_2Cl$), 3.52 (t, 1H, J, = 6Hz, $C\underline{H}_2OTBDMS$), 0.95 (s, 9H, $SiC(C\underline{H}_3)_3$), 0.15 (s, 6H, $Si(C\underline{H}_3)_2$); $\delta_C(CDCl_3)$ 69.02 (t, C-2), 50.33 (t, C-1), 31.01 (q, $C(C\underline{H}_3)_3$), 23.62 (s, $\underline{C}(CH_3)_3$), -4.6(q, $Si-(C\underline{H}_3)_2$. $\underline{M}/\underline{Z}$ (C.I. iBuH) 197/195 (M^+), 137, 91, 83.

Reaction of 4-tertbutyldimethylsiloxycyclohexanone (116) with 2-tertbutyldimethylsiloxyethylchloride with LDA

A solution of (116) (500mg, 2.2mmol) in dry THF (2ml) was added dropwise via a canula to a solution of LDA (1.1eq) at -78°C, stirred for ½ hr, 2-t-butyl-dimethylsiloxyethylchloride (430mg, 2.2mmol) in THF (2ml) was added dropwise via a canula. The solution was allowed to warm to room temperature, quenched with H_2O, THF evaporated off, partitioned between H_2O and ethyl acetate, washed with brine, dried (Na_2SO_4) and evaporated to yield 710mg of a slightly yellow oil, which was found to be only starting material.

Reaction of 4-t-butyldimethylsiloxycyclohexanone (116) and 2-t-butyldimethylsiloxyethylchloride with $KOBu^t$ in THF

Under a N_2 atmosphere using flame dried apparatus a slurry of $KOBu^t$ (300mg, 2.7mmol) was prepared in dry THF (10ml). To this was added dropwise a solution of (116) (500mg, 2.2mmol) in dry THF (2ml). The solution was stirred for 10 minutes and then 2-t-butyldimethylsiloxyethylchloride (430mg, 2.2mmol) in dry THF (2ml) was added dropwise. The mixture was stirred at 40-45° for 24 hours. Only starting materials were recovered.

4-t-butyldimethylsiloxy 2-(2'-propenyl)cyclohexanone (117)

A solution of LDA (1.1eq) was made and cooled to -78°C, where HMPT (0.6ml) was added and allowed to stir for 15 minutes. A solution of (116) (500mg, 2.2mmol) in dry THF (3mls), which had been azeotroped (x 3) with CCl_4 was added to the LDA solution and allowed to stir for 30 minutes. Allylbromide (distilled) (0.2ml, 2.2mmol) in THF (2ml) was added dropwise. The solution was allowed to warm up to room temperature and stirred overnight. Quenched with water THF evaporated and residue dissolved in ethyl acetate, washed with brine, dried (NA_2SO_4) and evaporated to yield 520mg. "Flash" chromatography using PE/EA (20:1) to yield 420mg (71%) as a mixture of cis and trans isomers. Found: C,67.1, H,10.5, calc. for $C_{15}H_{26}O_2Si$: C,67.4, H,10.2; ν_{max}(thin film) 1711 (C=O), 1639cm^{-1} (C=C); $\delta_H(CDCl_3)$ 5.65 (m, 1H, -C<u>H</u>=CH_2), 5.1 (m, 1H, CH=C<u>H</u>$_2$), 4.95 (m, 1H, CH=C<u>H</u>$_2$), 4.15 (m, 1H,

CHOTBDMS), 2.9-1.7 (m, 9H), 0.95 (s, 9H, Si-C$(CH_3)_3$), 0.15 (s, 6H, Si-$(CH_3)_2$); $\delta_C(CDCl_3)$ 212.61 (s), 210.94 (s), 136.33 (d), 136.04 (d), 116.55 (t), 116.20 (t), 69.32 (d), 65.60 (d), 46.76 (d), 43.87 (d), 40.84 (t), 40.44 (t), 38.34 (t), 36.77 (t), 35.47 (t), 35.02 (t), 33.77 (t), 33.04 (t), 25.76 (q), 18.09 (s), 18.04 (s), -4.87 (q), -4.68 (q); M/Z (iso-BuH C.I.) 269 (M^{+1}), 211, 177, 137, (100%) 133.

4-t-butyldimethylsiloxy 2-(2' ethanal) cyclohexanone (118)[129]

Osmium tetraoxide (∿20mg in 1.5ml ^tBuOH solution) was added to a mixture of (117) (250mg, 9.5mmol), ether (8ml) and H_2O (8ml) and the mixture was stirred at room temperature for 10 minutes. Then powdered sodium meta-periodate (450mg, 21mmol) was added over a 30 minute period and stirring was continued for 2.5 hours at R.T. The mixture was poured into H_2O (50ml) and extracted with ether (3 x 30ml). The organic extract was dried (Na_2SO_4) and evaporated to yield 470mg of a dark brown oil. Columned (medium pressure) PE/EA, 20:1 to yield 160mg (62%) of a colourless oil. Found: C,62.29; H,9.74. calc. for $C_{14}H_{26}O_3Si$: C,62.18, H,9.69%. ν_{max} 1710, 1695cm^{-1} (C=O), $\delta_H(CDCl_3)$ 9.8 (m, 1H, CHO), 4.15 (m, 1H, CHOTBDMS), 3.0-1.8 (m, 9H), 0.95 (s, 9H, Si-C$(CH_3)_3$) 0.15 (s, 6H, Si$(CH_3)_2$); M/Z (C.I., iBuH) 271 (M^{+1}), 213, 139 (100%), 75.

4-t-butyldimethylsiloxy 2-(2'-ethanal) cyclohexanone (118) with $NaBH_4$

Sodium borohydride (10mg, 0.18mmol) in absolute ethanol (5ml) was added to (118) (200mg, 0.74mmol) in THF (10ml). Solution stirred for 1 hour at R.T. and then poured into 2NHCl (5ml) and extracted with ether (3 x 10ml), washed with H_2O (1 x 10ml), brine (1 x 10ml), dried ($MgSO_4$) and evaporated to yield 153mg. Columned (medium pressure) PE/EA, 1:1 to yield 108mg (53%) of 4-t-butyldimethylsiloxy 2-(2'-hydroxy ethyl) cyclohexanone and 33mg (16%) of 4-t-butyldimethylsiloxy 2-(2'-hydroxy ethyl) cyclohexanol as a colourless oil. Found: C,61.38, H,11.31. calc. for $C_{14}H_{30}O_3Si$: C,61.26; H,11.02%. ν_{max} (film) 3450 (-OH). $\delta_H(CDCl_3)$ 4.15 (m, 1H), 3.6 (m, 3H, $C\underline{H}_2O\underline{H}$), 3.4 (br.s, 1H, $O\underline{H}$), 2.3-1.6 (m, 1OH), 0.95 (s, 9H, Si-C($\underline{Me}$)$_3$), 0.15 (s, 6H, Si-$(CH_3)_2$).

4-t-butyldimethylsiloxy 2-(2'-hydroxyethyl) cyclohexanone (119)[130]

Et_3N (0.55mmol, 0.08ml) in dry THF (5ml) under N_2 was added to formic acid (0.83mmol, 0.031ml), solution cooled at room temperature, $RuCl_2(Ph_3)_3$ (0.03mmol, 0.4%) added and allowed to evolve gas. 3 minutes later (118) (0.55mmol, 150mg) was added and stirred for approx. 30 minutes. Solution was then neutralised with 2NHCl, THF evaporated and residue dissolved in ether, washed with H_2O, dried (Na_2SO_4) and evaporated to give 155mg of a colourless oil. Columned (medium pressure) PE/EA 5:1

to give 110mg (73%) of a colourless oil. Found: C,61.82; H,10.43. calc. for $C_{14}H_{28}O_3Si$: C,61.72; H,10.36%. ν_{max} (film) 3450 (-OH), 1705cm^{-1} (C=O), $\delta_H(CDCl_3)$ 4.15(m, 1H, CHOTBDMS), 3.7 (m, 3H, CH_2OH), 2.5-1.6 (m, 9H), 0.95 (s, 9H, Si-C(Me)$_3$), 0.15 (s, 6H, Si-$(CH_3)_2$). M/Z (C.I. iBuH) 273 (M^{+1}), 215, 141.

4-hydroxy 2-(2'-hydroxyethyl) cyclohexanone (120)[132]

(119) (150mg, 0.55mmol) was dissolved in anhydrous THF (5ml) and tetrabutylammonium fluoride (0.16ml, 1.6mmol) was added and the solution stirred for 1 hour. THF evaporated off and the residue dissolved in ether and washed with brine, dried (Na_2SO_4) and evaporated to yield 86mg. Columned (medium pressure) PE/EA, 1:3 to yield 54mg (54%) of a colourless oil. Found: C,60.61, H,9.02. calc. for $C_8H_{14}O_3$; C,60.74, H,8.92%; $\nu_{max}(CHCl_3)$ 3455 (-OH), 1710 (C=O), $\delta_H(CDCl_3)$, 4.05 (m, 1H, CHOH), 3.7 (m, 3H, CH_2OH), 3.5 (br.s, 1H, OH), 2.5-1.6 (m, 9H); M/Z (C.I. iBuH) 159 (M^{+1}), 97.

4-hydroxy 2-(2'hydroxyethyl) cyclohexanone (120) with triphenyl phosphine and diethyl azodicarboxylate (DEAD)[133]

To a cooled solution of (120) (40mg, 0.25mmol), and triphenylphosphine (67mg, 0.25mmol) in anhydrous $CDCl_3$ (1ml) was added dropwise with stirring diethyl-azodicarboxylate (60mg, 0.34mmol) under an atmosphere of dry N_2. 'Hnmr of reaction mixture gave no indication of product.

1,5-Dichloropentan-3-one (125)[134]

3-chloropropionylchloride (124) (500g, 3.94mol) was added slowly to a stirred suspension of powdered anhydrous aluminium chloride (735g, 5.5mol) in DCM (550ml), contained in a cooled (ice-water bath) three-necked flask (31). Ethylene gas (dried over KOH and anhydrous $CaSO_4$) was bubbled into the reaction mixture, which was allowed to warm to 20°. The reaction was monitored by i.r. to ascertain completion. (A small quantity (∿0.1ml) of the mixture was treated with water (0.1ml), organic layer separated, dried ($MgSO_4$) and i.r. spectrum run, comparison of carbonyl stretching; starting material 1790cm^{-1}, product 1718cm^{-1}). The products were then slowly added to a cooled (ice-salt bath) mixture of dichloromethane (500ml), HCl and ice (2l of aqueous layer; ca 1M with respect to HCl), so that the temperature did not rise above 20° . The organic layer was separated, washed with water (3 x 2l) and dried ($MgSO_4$). The solvent was then evaporated under reduced pressure to yield crude 1,5 dichloropentan-3-one (540g, 88%) as a dark brown oil.

ν_{max} = 1718cm^{-1}; $\delta_H(CDCl_3)$ 3.73 (t, J=6.5Hz, 4H), 3.5 (t, J=6.5Hz, 4H).

Tetrahydro-4H-pyran-4-one (121)[135]

A 3l three-necked round-bottomed flask, fitted with an efficient mechanical stirrer, a reflux condenser and

a 250ml dropping funnel was charged with sodiumdihydrogen phosphate dihydrate (624g, 4mol), 88% orthophosphoric acid (196g, 1.76mol) and water (1.25l). The reaction vessel was immersed in a water bath and heated until the temperature of its contents reached 100°. Crude 1,5-dichloropentan-3-one (125) (310g, 2mol) was placed in the dropping funnel and added dropwise over a period of 75min to the vigorously stirred aqueous solution, which was maintained at 100° ± 3°. The temperature of the reactants was maintained at 100° for a further 120min and was then cooled to 0°. 10M sodium hydroxide (aq) (∿650ml) was then added slowly to the cooled products (ice/water bath) until the pH had risen to 5-6. The neutralised products were decanted from the tarry residue and extracted with dichloromethane (500ml + 2x250ml). The combined extracts were dried ($MgSO_4$) concentrated under reduced pressure (rotary evaporator) and the pale brown residual liquid rapidly distilled under reduced pressure to yield a colourless liquid. Tetrahydro-4H-pyran-4-one (91g, 45%); b.p. 58°/12mm (lit,[135] 59-60°, 13mmHg).

ν_{max} (thin film) 1719cm^{-1} (C=O). $\delta_H(CDCl_3)$ 3.98 (t, 3H, J=6Hz. $C\underline{H}_2$-O-$C\underline{H}_2$), 2.51 (t, 3H, J=6Hz-$C\underline{H}_2$-C-$C\underline{H}_2$).

G.L.C. (CPSIL-5, 80°) 98.5% pure.

2,3-Dihydro-4-morpholino-2H-pyran (129)

Under a N_2 atmosphere, a mixture of tetrahydro-4H-pyran-4-one (121) (3g, 0.03mol), morpholine (2.55g,

0.06mol) and benzene (30ml) were refluxed. Water was separated by means of a Dean and Stark apparatus (∿4hrs). Solvent removed on rotary evaporator. Residue distilled on Kugelrohr to yield 4.65g (92%) of a white crystalline solid (mp 42-43°) (lit,[169] b.p. 62-64° at 0.1mm Hg). ν_{max} (thin film) 1650 (C=C), 1450cm^{-1} (C-O-C); $\delta_H(CDCl_3)$ 4.58 (t, 1H, J=3Hz, C=C$\underline{H}$), 4.20 (m, 2H, C=CC$\underline{H}_2$O), 3.73 (m, 6H, C$\underline{H}_2$OC$\underline{H}_2$ and C$\underline{H}_2$O), 2.81 (m, 4H, C$\underline{H}_2$NC$\underline{H}_2$), 2.13 (m, 2H, C$\underline{H}_2$C=C).

6-morpholino 3-oxabicyclo[3.3.1]nonan-9-one (133)[142]

Acrolein (0.54g, 0.65ml) was added over 30min to a solution of (129) (1.64g, 9.8mmol) in benzene (30ml), maintained at 0°. Stirring of the cold solution was continued for an additional 1hr, after which the mixture was heated at reflux for 3 hrs. The benzene was evaporated and the product collected by distillation on the Kugelrohr (b.p. 120°, 0.15mm Hg) to yield 1.62g (74%) of a pale yellow oil as a mixture of exo and endo isomers [G.C. (71.29) OV column 175°]. Found: C,64.12, H,8.43 N,6.32, $C_{12}H_{19}NO_3$ requires: C,63.98, H,8.50, N,6.22%. ν_{max} (thin film) 1717cm^{-1} (C=O), $\delta_H(CDCl_3)$ 4.2-3.6 (m, 8H, C$\underline{H}_2$OC$\underline{H}_2$, C$\underline{H}_2$OC$\underline{H}_2$), 2.85 (m, 1H, C$\underline{H}$-N), 2.5 (m, 4H, C$\underline{H}_2$NC$\underline{H}_2$), 2.3-1.8 (m, 6H). $\underline{M}/\underline{Z}$ (70ev. E.I.) 225 (M^+), 126 (100%), 28.

6-morpholino 3-oxabicyclo[3.3.1]nonane (134)

(133) (0.5g, 2.2mmol) was refluxed with 0.36ml hydrazine (99-100%) and potassium hydroxide (0.42g) in triethylene glycol (5ml) for 1.5hrs. Then the mixture was distilled until a bottom temperature of 190° was reached. The residue was then refluxed for 3 hrs. The residue and distillate were combined and diluted with H_2O (10ml), extracted with ether (3x20ml), washed with brine (2x30ml), dried ($MgSO_4$), solvent evaporated and product distilled on the Kugelrohr (120° , 0.3mmHg) to yield 0.33g (72%) of a pale green oil, which was a mixture of exo and endo isomers. [G.C.(91.9) OV column 175°]. Found: C,67.90, H,10.01, N,6.59, $C_{12}H_{21}NO_2$ requires C,68.21, H,10.02, N,6.63%. $\delta_H(CDCl_3)$ 4.2-3.6 (m, 8H, $C\underline{H}_2OC\underline{H}_2$, $C\underline{H}_2OC\underline{H}_2$), 2.85 (m, 1H, $C\underline{H}$-N), 2.5 (m, 4H, $C\underline{H}_2$-N-$C\underline{H}_2$), 2.3-1.6 (m, 8H). M/Z (70ev E.I.) 211 (M^+), 126 (100%), 100,87.

N-oxide of 6-morpholino 3-oxabicyclo[3.3.1]nonane (135)[142]

To a solution of (134) (150mg, 0.7mmol), ethanol (1.5ml), methanol (1.5ml) was added 30% H_2O_2 (1ml). The resulting solution was heated at 70-72° for 36 hours. The excess H_2O_2 was decomposed by stirring the solution for 8 hours in the presence of platinum black, filtered and evaporated to give a colourless viscous syrup. This was dried at 80° (1mm) to give a colourless crystalline solid.

Pyrrolysis of the N-oxide of 6-morpholino 3-oxabicyclo [3.3.1]nonane (135)[142]

Apparatus was set up for simple distillation, flushed with nitrogen, and heated slowly. At 115° liquification occurred. After 1hr at 115° the flask was heated at 150° for 3 hrs. However, examination of the distillate and residue showed no traces of the desired product.

N-oxide of 6-morpholino 3-oxabicyclo[3.3.1]nonane (135) with 4Å molecular sieves in THF[141]

Hydrated (135) (100mg) was dissolved in dry THF (10ml), 4Å molecular sieves were added and the H_2O was removed at 80°. The solution was left at this temperature for 24hrs. It was then diluted with ether, filtered evaporated to yield 60mg of a yellow oil, which contained none of the desired compound.

N-oxide of 6-morpholino 3-oxabicyclo[3.3.1]nonane (135) with 4Å molecular sieves in DMSO[141]

Hydrated (135) (140mg) was dissolved in dry DMSO (10ml), 4Å molecular sieves were added and the solution stirred at room temperature for 24hr. It was then diluted with ether, filtered, washed with water, dried ($MgSO_4$) and evaporated to yield 80mg of a yellow oil, which contained none of the desired compound.

2,3-Dihydro-4-pyrrolidinyl-2H-pyran (122)

In an N_2 atmosphere, a mixture of (121) (120g, 1.2mol), pyrrolidine (272ml) was refluxed in benzene (800mls). Water was separated by means of a Dean-Stark trap. After water had ceased to separate, the benzene was evaporated off and the residue azeotroped twice with benzene to remove excess pyrrolidine to yield 172g (94%), which was used without purification.

ν_{max} ($CHCl_3$) 1645 (C=C), 1450cm^{-1} (C-O-C); δ_H($CDCl_3$) 4.6 (t, 1H, J=3Hz, C=C<u>H</u>), 4.2 (m, 2H), 3.8 (m, 2H), 2.81 (m, 4H, $C\underline{H}_2NC\underline{H}_2$), 2.2-1.8 (m, 5H).

Exo and endo 6-hydroxy 3-oxabicyclo[3.3.1]nonan-9-one (147) and (148)

(122) (4.39g, 0.029mol) was dissolved in THF (75ml) and purged with N_2. The solution was stirred in an N_2 atmosphere and cooled to below 10°, H_2O (0.8ml) was added, followed immediately by acrolein (2.9ml, 0.044mol) dropwise. The reaction was stirred at room temperature for 2hr, after which dilute HCl was added until pH1-2 had been reached. The reaction was then stirred for 30min, after which ether was added and stirring continued for 10min. The batch was allowed to settle for 10-15min, after which the aqueous layer was run off. The aqueous layer was extracted with ether (3x50ml). The organic layer was washed with H_2O (1x50ml), brine (1x50ml). Each of these washes was back extracted with the ether extracts used for the main aqueous. Ether extracts were combined,

dried ($MgSO_4$), the solvent evaporated to yield 2.6g (57%) of 6-hydroxy 3-oxabicyclo[3.3.1]nonan-9-one as a mixture of exo and endo isomers. [G.C. (1:1) OV column 175°C.] Isomers separated on the Chromatotron (PE/EA, 2:1) Endo isomer (148) eluted first as a colourless oil

Endo isomer: ν_{max} ($CHCl_3$) 3460, 3450 (-OH), 1720 (C=O), 1080cm^{-1}. δ_H($CDCl_3$) 4.6 (septet, 1H, CHOH), 4.27 (dt, 1H, J_{2e-2a} = 11.28Hz, J_2 = 1.6Hz), 4.18 (dt, 1H, J_{4e-4a} = 11.72Hz, J_2 = 1.5Hz), 3.88 (dt, 1H, J_{2a-2e} = 11.28Hz, J_2 = 2.1Hz), 3.83 (dd, 1H, J_{4a-4e} = 11.72Hz, J_2 = 2.8Hz), 2.75 (m, 1H), 2.48 (octet, 1H), 2.375 (m, 2H), 2.10 (m, 1H), 1.74 (m, 1H), 1.72 (m, 1H, -OH). δ_C($CDCl_3$) 212.65 (s, C-9), 74.96 (d, C-6), 74.48 (t, C-2), 68.70 (t, C-4), 57.41 (d, C-5), 48.46 (d, C-1), 30.44 (t, C-7), 27.246 (t, C-8). M/Z (70ev. E.I.) 156 (M^+), 138, 111, 97, 83, 71, 55, 54, 41, 28, 27. M/Z 156.0781 (M, 44%, calculated for $C_8H_{12}O_3$ 156.0786).

Exo isomer (147) after further elution as colourless crystals. m.p. 184.5-185°. Exo isomer: ν_{max}($CHCl_3$) 3460, 3450 (-OH), 1720 (C=O), 1080cm^{-1}. δ_H($CDCl_3$) 4.6 (dt, 1H, J_{4e-4a} = 11.56Hz, J_2 = 1.48Hz), 4.2 (dt, 1H, J_{2e-2a} = 11.32Hz, J_2 = 1.6Hz), 4.11 (m, 1H, CHOH), 3.91 (dt, 1H, J_{2a-2e} = 11.32Hz), 3.73 (dq, 1H, J_{4a-4e} = 11.56Hz, J_2 = 2.4Hz, J_3 = 1.1Hz), 2.57-2.45 (m, 2H), 2.35 (septet, 1H), 2.11 (m, 1H), 2.02 (m, 1H), 1.83-1.79 (m, 2H). δ_C($CDCl_3$) 214.11 (s, C-9), 76.53 (d, C-6), 75.67 (t, C-2), 70.94 (t, C-4), 57.38 (d, C-5), 49.87 (d, C-1), 29.22 (t, C-7 and 8). M/Z (70ev.E.I.) 156 (M^+), 138, 111,

97, 83, 71, 55, 54, 41, 28, 27 M/Z (E.I.) 156.0785 (M, 32%, calculated for $C_8H_{12}O_3$ 156.0786).

The acidic aqueous layer was basified, extracted with ether (3x30ml), washed with H_2O (30ml), brine (30ml) to yield 0.84g of a gum which was filtered through silica gel to yield 0.15g of 6-pyrrolidinyl 3-oxabicyclo[3.3.1] nonan-9-one (123) as a mixture of exo and endo isomers. ν_{max} (thin film) 1726cm^{-1} (C=O), $\delta_H(CDCl_3)$ 4.2-3.7 (m, 4H, CH_2-O-CH_2), 2.9 (m, 1H), 2.5 (m, 4H, CH_2-N-CH_2) 2.3-1.6 (m, 10H). M/Z (70ev.E.I.) 209 (M^+), 126 (100%).

6-oxo 3-oxabicyclo[3.3.1]non-6-ene (Method A) (149)[146]

(147) and (148) (200mg, 1.3mmol) in ether (3ml) was cooled in an ice/salt bath and added dropwise via a cannula to a cooled (ice/salt bath) solution of cH_2SO_4 (1.2ml) over a period of 30 minutes. Then stirred for 1 hour, solution poured into ice (6g) extracted with ether (3x20ml), washed with H_2O (10ml), brine (10ml), dried (Na_2SO_4) and filtered through a column of Florisil to yield 26mg (16%) of a colourless waxy solid.

6-oxo 3-oxabicyclo[3.3.1]non-6-ene (Method B) (149)

(147) and (148) (100mg, 0.65mmol) was dissolved in 85% phosphoric acid (2ml) and heated at 150° for 1½hr. The cooled reaction mixture was diluted with H_2O and extracted with pentane, washed with sodium carbonate (aq), brine (2x15ml) and dried (Na_2SO_4) and evaporated to give a yellow oil (30mg), which contained product with several other components.

6-oxo 3-oxabicyclo[3.3.1]non-6-ene (Method C) (149)[148]

A solution of (153) (100mg, 0.42mmol) in glacial acetic acid (10ml of 0.5M sodium acetate to which 1% acetic anhydride had been added) was placed in a stoppered flask and thermostatted at 50° for 24hr. The cooled mixture was poured onto ice-water (30ml), extracted with pentane (3x30ml), and the combined extracts washed once with H_2O, then with sat sodium hydrogen carbonate solution

until no further carbon dioxide evolution was observed. The pentane solution was then dried (Na_2SO_4) and pentane evaporated to yield a yellow oil (20mg), columned (PE/EA, 5:1) to yield 16mg (27%).

6-oxo 3-oxabicyclo[3.3.1]non-6-ene (Method D) (149)

(153) (200mg, 0.84mmol) was dissolved in collidine (4ml) and refluxed for 20 hr. The cooled solution was acidified with cHCl (congo red), extracted with ether (3x20ml), dried ($MgSO_4$) and evaporated to yield a yellow oil (70mg), columned (PE/EA, 5:1) to yield 49mg (42%).

6-oxo 3-oxabicyclo[3.3.1]non-6-ene (Method E) (149)[149]

(154) (700mg, 4mmol), LiBr (1.04g, 12mmol), Li_2CO_3 (890mg, 12mmol) were dissolved in dry DMF (10ml) under an N_2 atmosphere. The solution was stirred at 150° for 5hr, then poured into H_2O (30ml), extracted with ether (3x20ml), washed with brine and dried (Na_2SO_4) and evaporated to yield 600mgs of a yellow oil. Flash chromatography (PE/EA, 5:1) yielded 370mg (67%) of a waxy colourless solid.

6-oxo 3-oxabicyclo[3.3.1]non-6-ene (Method F) (149)[150]

(152) (1g, 5mmol), LiCl (0.55g, 13mmol) and Li_2CO_3 (0.5g, 6.8mmol) were dissolved in N-methyl pyrrolidone (5ml) under an N_2 atmosphere. Using an oil bath, the temperature was slowly raised to 85° and then heated at this temperature for 2 hr, then cooled, poured into

H_2O, and extracted with ether (3x20ml), washed with brine, dried (Na_2SO_4) and azeotroped with CCl_4 (3x25ml) to yield 1.2g of a brown oil. Flash chromatography (PE/EA, 5:1) to yield 480mg (70%). ν_{max} (CH_2Cl_2) 3031 (=CHSt), 1728 (C=O), 1648cm^{-1} (C=CSt) $\delta_H(CDCl_3)$ 6.01 (dt, 1H, J_1=9.5Hz, J_2=3.3Hz, = C<u>H</u> (C-6)), 5.7 (qt, 1H, J_1=9.5Hz, J_2=6Hz, J_3=1.9Hz, =C<u>H</u> (C-7)), 4.15 (dt, 1H, J_{4e-4a}=11.2Hz, J_2=1.8Hz), 3.94 (dt, 1H, J_{2e-2a}=10.8Hz, J_2=1.83Hz), 3.79 (dd, 1H, J_{4a-4e}=11.2Hz, J_2=1.46Hz), 3.71 (dd, 1H, J_{2a-2e}= 10.8Hz, J_2=1.83Hz), 2.81 (m, 3H, C<u>H</u>$_2$-CH=CH and =CH-C<u>H</u> (bridgehead)), 2.54 (m, 1H, bridgehead). $\delta_C(CDCl_3)$ 210.58 (s, C-9), 131.01 (d, C-6), 125.08 (d, C-7), 76.81 (t, C-4), 72.25 (t, C-2), 50.16 (d, C-5), 48.45 (d, C-1), 36.58 (t, C-8). <u>M/Z</u> (70ev. E.I.) 138 (M^+, 100%), 108, 79. <u>M/Z</u> 138.0673 (M, 100%, calculated for $C_8H_{10}O_2$ 138.0679).

<u>Reaction of exo and endo 6-hydroxy 3-oxabicyclo[3.3.1] nonan-9-one (147) and (148) with phosphorus oxychloride and pyridine</u>[147]

A solution of (147) and (148) (200mg, 1.3mmol) in dry benzene (2ml) was added to a stirred solution of phosphorus oxychloride (0.18ml, 1.9mmol) and pyridine (1.54ml, 1.9mmol) in dry benzene under N_2 at room temperature overnight. The reaction quenched with H_2O (10ml), washed with sat $CuSO_4$ (aq), brine and dried ($MgSO_4$) and evaporated to yield 180mg of a yellow oil. Columned (PE/EA, 5:1) to yield 40mg of a waxy solid, <u>3-oxabicyclo[3.3.1]non-6-en-9-one</u> (149); 60mg of <u>endo</u>

6-chloro 3-oxabicyclo[3.3.1]nonan-9-one(151); ν_{max} ($CHCl_3$) 1720cm^{-1} (C=O), δ_H($CDCl_3$) 4.82 (sextet, 1H, CHCl), 4.28 (dt, 1H, J_{GEM}=11.5Hz, J_2=1.5Hz), 4.24 (dt, 1H, J_{GEM}=12Hz, J_2=1.5Hz), 3.90 (dt, 1H, J_{GEM}=11.5Hz, J_2=2.2Hz), 3.86 (dd, 1H, J_{GEM}=12Hz, J_2=2.75Hz), 3.08 (m, 1H), 2.7 (m, 1H), 2.44 (m, 1H), 2.15 (m, 2H), 2.0 (m, 1H). δ_C($CDCl_3$) 210.12 (s, C-9), 76.69 (t, C-2), 74.42 (t, C-4), 61.92 (d, C-6), 56.87 (d, C-5), 49.44 (d, C-1), 28.56 (t, C-7), 27.73 (t, C-8). M/Z (70 ev. E.I.) 176/174 (M^+), 139, 109, 81, 67, 55 (100). Found: C,54.91; H,6.42. $C_8H_{11}ClO_2$ requires C,55.02; H,6.35%; 60mg of exo 6-chloro 3-oxabicyclo [3.3.1]nonan-9-one (150). ν_{max}($CHCl_3$) 1720cm^{-1} (C=O), δ_H($CDCl_3$) 4.73 (dt, 1H, J_{GEM}=12Hz, J_2=1.5Hz), 4.35 (m, 1H, CHCl), 4.23 (dt, 1H, J_{GEM}=11.36Hz, J_2=1.6Hz), 3.92 (dt, 1H, J_{GEM} = 12Hz, J_2=2.2Hz), 3.79 (dt, 1H, J_{GEM} = 11.9Hz), 2.88 (m, 1H),2.64 (m, 1H), 2.4 (m, 1H), 2.2 (m, 2H), 1.9 (m, 1H). δ_C($CDCl_3$) 210.16 (s, C-9), 76.65 (t, C-2), 72.76 (t, C-4), 64.92 (d, C-6), 57.88 (d, C-5), 48.81 (d, C-1), 32.15 (t, C-7), 29.77 (t, C-8). M/Z (70ev. E.I.) 176/174 (M^+), 138 (100), 109, 81, 55. Found: C, 55.12; H,6.29, $C_8H_{11}ClO_2$ requires C,55.02; H,6.35%.

6-nitrooxy 3-oxabicyclo[3.3.1]nonan-9-one (152)[150]

Fuming HNO_3 (19.1ml) was added to acetic anhydride (39ml) whilst cooling in an IMS/CO_2 bath, keeping the temperature below -25°. Stirred for 10min, after which (147) and (148) (2.3g, 14.7mmol) in acetic anhydride

(2ml) was added dropwise, stirred for 1-2hr (followed by TLC) and then poured into H_2O and stirred overnight (to decompose acetic anhydride), extracted with ether (3x30ml), washed with brine, dried (Na_2SO_4) and evaporated to yield an orange oil. Columned (PE/EA, 4:1) to yield 2.8g (78%) of colourless crystals as a mixture of exo and endo isomers. (Recrystallised PE/EA) M.P. 65.9-67.0°, $\nu_{max}(CH_2Cl_2)$ 1735 (C=O), 1629 (NO_2 st as), 1219cm^{-1} (NO_2 st sy). $\delta_H(CDCl_3)$ 5.62 (m, 1H, C<u>H</u>ONO$_2$, equatorial), 5.25 (m, 1H, C<u>H</u>ONO$_2$, axial), 4.28 (m, 4H, C<u>H</u>$_2$OC<u>H</u>$_2$), 3.94 (m, 4H, C<u>H</u>$_2$OC<u>H</u>$_2$), 2.8 (m, 4H), 2.5-1.8 (m, 8H). Found: C,47.71, H,5.55, N,6.82. $C_8H_{11}NO_5$ requires C,47.76, H,5.51, N,6.96%.

<u>3-oxabicyclo[3.3.1]nonan-6-yl methane sulphonate-9-one(153)</u>

To a stirred solution of (147) and (148) (200mg, 1.3mmol), Et_3N (0.26ml, 1.8mmol) in dry DCM (5ml) at 0° was added dropwise over 15min a solution of methane sulphonylchloride (0.12ml, 1.6mmol) in dry DCM (2ml). The resulting solution was stirred for 2hr at 0° . The reaction was quenched with H_2O. The organic phase was separated, washed with 2MHCL, brine and dried ($MgSO_4$). Evaporation of solvent gave 310mg of a yellow oil. Columned (PE/EA, 3:1) to give the mesylate as a waxy solid (260mg, 86%) as a mixture of exo and endo isomers (1:1).

$\nu_{max}(CHCl_3)$ 1720cm^{-1} $\delta_H(CDCl_3)$ 5.2 (m, 1H, C<u>H</u>OMs (EqH)), 4.3 (m, 1H, CHOMs (AxH)), 4.1-3.6 (m, 4H, C<u>H</u>$_2$-

O-C$\underline{H}_2$), 3.0 (s, 3H, -$SO_2C\underline{H}_3$), 2.7 (m, 1H), 2.4 (m, 2H), 2.2-1.8 (m, 4H). $\underline{M}/\underline{Z}$ (70ev. E.I.) 234 (M^+), 138 (100%), 109, 79, 55 (100%). $\underline{M}/\underline{Z}$ (E.I.) 234.0556 (M, 7.5% calculated for $C_9H_{14}O_5S$ 234.0561).

6-bromo 3-oxabicyclo[3.3.1]nonan-9-one (154)

(153) (1.9g, 8.1mmol) and lithium bromide (1.7g, 19.4mmol) were heated under reflux in analar acetone (30ml) for 48hr. The suspension was concentrated, then diluted with ether, washed with H_2O, brine and dried ($MgSO_4$) and evaporated to give 1.28g of a brown oil, passed through a column of Florisil to yield 1.14g (64%) of a yellow oil as a mixture of exo and endo isomers. ν_{max} (thin film) 1710cm^{-1} (C=O); $\delta_H(CDCl_3)$ 4.91 (sextet, 1H, C$\underline{H}$Br, equatorial), 4.75 (dt, 1H, C$\underline{H}_2$O), 4.45 (m, 1H, C$\underline{H}$Br, axial), 4.31-4.22 (m, 3H, C$\underline{H}_2$O) 4.0-3.8 (m, 4H, C$\underline{H}_2$O), 3.21-2.95 (m, 2H), 2.8 (m, 1H), 2.7 (m, 1H), 2.45 (m, 3H), 2.3-1.9 (m, 3H). $\underline{M}/\underline{Z}$ (70ev. E.I.) 221/219 (M^+), 139 (100), 109, 81, 55. Found: C,43.95; H,5.13, $C_8H_{11}BrO_2$ requires C,43.86; H, 5.06%.

Ethylenethioketal of 6-hydroxy 3-oxabicyclo[3.3.1]nonan-9-one (155)

To a 0° solution of (147) and (148) (9.5g, 0.061mol) and ethanedithiol (9.5ml, 0.09mol) in N_2 atmosphere in dry DCM (20ml) was added $BF_3.Et_2O$ (1.9ml, 0.012mol) dropwise. The reaction mixture was stirred for 20min, warmed to room temperature and stirred an additional

2hr. The solvent evaporated and the residue columned (Dry column "flash" chromatography, PE/EA, 10:1) directly to yield 12.2g (86%) of a colourless oil as a mixture of exo and endo isomers. $\delta_H(CDCl_3)$ 4.18 (m, 1H), 4.17-4.06 (m, 2H), 3.95 (m, 1H), 3.87 (m, 1H), 3.88 (dd, 1H), 3.35-3.13 (m, 4H, -S-$\underline{CH}_2$-CH_2-S), 2.47 (m, 1H), 2.31 (m, 1H), 2.05 (m, 1H), 1.91 (m, 2H), 1.72 (m, 1H). $\underline{M}/\underline{Z}$ (70ev. E.I.) 232 (M^+), 214 (100%), 131, 105. Found: C,51.74, H,6.91. $C_{10}H_{18}O_2S_2$ requires C,51.69, H,6.94%.

Exo and endo 6-hydroxy 3-oxabicyclo[3.3.1]nonane (156) and (157) Method A.[153]

(155) (700mg, 3mmol), hydrazine hydrate (98%) (3ml), potassium hydroxide (1.4g, 2 parts by weight) dissolved in Trigol (10ml). These were heated in a simple distillation apparatus, when the internal temperature reached the range 90-135° , evolution of gas occurred. Heating was continued until the temperature reached 190° and maintained at that temperature until final completion. Reaction followed by t.l.c. Reaction cooled, diluted with brine, extracted with ether (6x30ml), washed with brine, dried (Na_2SO_4) and evaporated to yield 230mg of a yellow oil. Columned (medium pressure) PE/EA. 2:1 to give 120mg (28%) of a colourless oil as a mixture of exo and endo isomers (1:1).

Exo and endo 6-hydroxy 3-oxabicyclo[3.3.1]nonane (156) and (157) Method B[154]

Liquid NH_3 (50ml) was introduced into a 100ml three necked flask equipped with dry ice condenser. With stirring under N_2, sodium metal (50mg) was added giving the solution a dark blue colour. After 15 min, the colour remained indicating the liq NH_3 and the apparatus to be dry. So with cooling in a dry ice/IMS bath, the sodium (1.47, 0.064mol) was added over a period of 5min, then stirring continued for 30min. (155) (1.65g, 0.0071mol) was added in anhydrous THF (5ml) over 10min, keeping internal temp at approximately -40° . Stirring was continued at this temperature for 1½hr. Then dry aceto-nitrile (4ml) was introduced (care-effervescence) over 10min, the cooling bath was removed and the liq NH_3 allowed to evaporate. H_2O (20ml) added and then residue extracted with ether (3x50ml), dried (Na_2SO_4) and evaporated to give 430mg (43%) of a colourless oil as a mixture of exo and endo isomers.

Exo and endo 6-hydroxy 3-oxabicyclo[3.3.1]nonane (156) and (157) Method C[155]

Raney nickel (W-2), (50% slurry in H_2O (pH-10)) was washed with H_2O until neutral, then 95% ethanol (3x50ml), absolute ethanol (3x50ml). Approx. 7g Raney nickel was suspended in absolute ethanol (30ml), (155) (1g, 4.3mmol) in absolute ethanol (5ml) was added and the resulting solution refluxed for 30min. The solution

was filtered and passed through a small plug of Florisil to yield 460mg (76%) as a colourless oil, which was a mixture of exo and endo isomers in an approximately 1:1 ratio. Separated by flash chromatography (PE/EA, 4:1). Endo isomer eluted first as a colourless oil.

Endo isomer: $\nu_{max}(CHCl_3)$ 3460, 3450 (-OH), 1080cm^{-1} $\delta_H(CDCl_3)$ 4.09 (m, 1H, C<u>H</u>OH), 3.88 (dt, 1H, J_{GEM}=11Hz), J_2=2Hz), 3.83 (dt, 1H, J_{GEM}=11.5Hz, J_2=2Hz), 3.74 (dt, 1H, J_{GEM}=11Hz, J_2=2Hz), 3.71 (dd, 1H, J_{GEM}=11.5Hz, 2.6Hz), 2.49 (m, 1H), 2.13 (m, 1H), 1.8 (m, 1H), 1.7 (m, 2H), 1.6 (m, 3H), 1.4 (m, 1H, CHO<u>H</u>). $\delta_C(CDCl_3)$ 73.38 (t, C-2), 70.58 (d, C-6), 69.56 (t, C-4), 36.33 (d, C-5) 31.14 (t, C-9) 30.91 (t, C-7), 29.34 (d, C-1) 28.33 (t, C-8). <u>M</u>/<u>Z</u> (70ev. E.I.) 142 (M^+), 124, 92, 79, 67, 55, 41. Found: C,67.72; H,9.89. $C_8H_{14}O_2$ requires C,67.67%, H,9.93%.

Exo isomer: $\nu_{max}(CHCl_3)$ 3460, 3450 (-OH), 1080cm^{-1} $\delta_H(CDCl_3)$ 4.19 (dt, 1H, J_{GEM}=11.8Hz, J_2=1.5Hz), 3.98 (m, 1H, C<u>H</u>OH), 3.85 (dt, 1H, J_{GEM}=11Hz , J_2=2Hz), 3.71 (dt, 1H, J_{GEM}=11Hz, J_2=2.15Hz), 3.6(dq, 1H, J_{GEM}=11.8Hz, J_2=2.3Hz, J_3=1.15Hz), 2.45 (m, 1H), 2.18 (m, 1H), 1.9 (m, 2H), 1.7 (m, 1H), 1.6 (m, 2H), 1.5 (bs, 1H, CHO<u>H</u>). $\delta_C(CDCl_3)$ 73.04 (t, C-2), 72.91 (d, C-6), 66.48 (t, C-4), 36.14 (d, C-5), 31.76 (t, C-9), 30.32 (t, C-7), 29.39 (t, C-8), 28.55 (d, C-1). <u>M</u>/<u>Z</u> (70ev. E.I.) 142 (M^+), 124, 92, 79, 67, 55, 41. Found: C,67.73; H,9.91. $C_8H_{14}O_2$ requires C,67.67%, H,9.93%.

3-oxabicyclo[3.3.1]nonan-6-one (158)[156]

Pyridiniumchlorochromate (910mg, 4.2mmol) was suspended in DCM (5ml) and (156) and (157) (400mg, 2.8mmol) in DCM (2ml) was rapidly added at R.T. The solution became briefly homogeneous before depositing the black insoluble reduced reagent. After 1-2hr the oxidation followed by t.l.c. was complete. The black reaction mixture was diluted with 5 volumes of anhydrous ether, the solvent decanted and the black solid washed twice with ether. Product was isolated simply by filtration of the organic extracts through Florisil and evaporation of the solvent at reduced pressure to yield 310mg (79%) of a colourless waxy oil/solid. $\nu_{max}(CHCl_3)$ 1705cm^{-1} (C=O), $\delta_H(CDCl_3)$ 4.03 (d, 1H, J_{GEM}=11.2Hz), 3.91 (dt, 1H, J_{GEM}=11.4Hz, J_2=2.2Hz), 3.84 (dt, 1H, J_{GEM}=11.4Hz, J_2=2.2Hz), 3.72 (dd, 1H, J_{GEM}=11.4Hz, J_2=2.2Hz), 2.85 (m, 1H), 2.55 (m, 2H), 2.2-1.95 (m, 5H). $\delta_C(CDCl_3)$ 213.86 (s, C-6), 73.84 (t, C-2), 69.40 (t, C-4), 47.18 (d, C-5), 40.57 (t, C-7), 31.76 (t, C-9), 29.72 (t, C-8), 28.63 (d, C-1). M/Z (iBuH. C.I.) 141 (M^{+1}), 95, 81. Found: C,68.16; H,8.72. $C_8H_{12}O_2$ requires: C,68.55; H,8.63%.

Ethylene thioketal of 3-oxabicyclo[3.3.1]non-6-en-9-one (159)

To a O° solution of (149) (200mg, 1.45mmol) and ethanedithiol (0.2ml, 1.9mmol) in N_2 atmosphere in dry DCM (5ml) was added $BF_3.Et_2O$ (0.08ml, 0.5mmol) dropwise. The reaction mixture was stirred for 20min, warmed to

room temperature and stirred an additional 2hr. The solvent was evaporated and the residue columned (PE/EA, 10:1) directly to yield 240mg (77%) of a colourless oil. $\nu_{max}(CHCl_3)$ 3030 (=CHst), 1650cm^{-1} (C=Cst) $\delta_H(CDCl_3)$ 6.0-5.7 (m, 2H, C<u>H</u>=CH), 4.05 (m, 2H, C<u>H</u>$_2$O), 3.8 (m, 2H, CH_2O), 3.4 (m, 4H, -SCH_2CH_2S-), 2.85 (m, 3H, C<u>H</u>$_2$ -CH=CH and =CH-C<u>H</u> (bridgehead), 2.5 (m, 1H, bridgehead). <u>M</u>/<u>Z</u> (70ev. E.I.) 214(M^+), 131, 105, 91. Found: C,55.79, H,6.43. $C_{10}H_{14}OS_2$ requires C,56.04, H,6.58%.

3-oxabicyclo[3.3.1]non-6-ene (28) Method A[140]

To a solution of (149) (200mg, 1.5mmol), KOH (200mg) in diethylene glycol (5ml) was added 0.2ml of 98% hydrazine hydrate. After refluxing for 1hr, the apparatus was set up for a distillation, and distilled until the temperature had reached 195°-200°. Then refluxing was continued for 3hrs. Distillate and residue combined and poured into ice/H_2O, acidified and then extracted with ether, washed with brine, dried ($MgSO_4$) and evaporated to yield 130mg of a yellow oil. Columned (medium pressure) PE/EA 5:1 to yield 23mg (12%) of a colourless oil.

3-oxabicyclo[3.3.1]non-6-ene (28) Method B[157]

(161) (110mg, 0.5mmol) was dissolved in freshly distilled DBU (0.25ml, 1.6mmol) in an N_2 atmosphere. Solution heated at 70° for 2hr. The solution was cooled and diluted with DCM (10ml), washed with H_2O (10ml), MH_2SO_4 (10ml) and H_2O (10ml), dried (Na_2SO_4) and evaporated. Residue dissolved in ether and passed down a column of Florisil to yield 24mg (39%) of a colourless oil.

3-oxabicyclo[3.3.1]non-6-ene (28) Method C[158]

(158) (100mg, 0.72mmol) in anhydrous ether (1ml) was added to a rapidly stirred suspension of zinc (dust) (480mg, 7.2mmol) and chlorotrimethylsilane (400mg, 3.6mmol) in anhydrous ether (10ml). Then placed in a temperature controlled oil bath (40°) for 72hr. Solution cooled, mixture filtered and the etheral solution washed with

$NaHCO_3$ (aq) and dried (Na_2SO_4) to yield 60mg of a slightly yellow oil. Columned (medium pressure) PE/EA, 5:1 to yield 37mg (41%) of a colourless oil. ν_{max} ($CHCl_3$) 3030 (=CHSt), 1640cm^{-1} (C=CSt), δ_H ($CDCl_3$) 5.9 (m, 1H, =C<u>H</u>), 5.6 (m, 1H, =C<u>H</u>), 4.05-3.6 (m, 4H, C<u>H</u>$_2$OC<u>H</u>$_2$), 2.45 (m, 1H), 2.3 (m, 2H), 1.95 (m, 3H). M/Z (70ev E.I.) 124 (M^+), 93, 92, 67. <u>M/Z</u> 124.0879 (M, 100%, calculated for $C_8H_{12}O$ 124.0887).

<u>Attempted desulphurisation of the ethylene thioketal of 3-oxabicyclo[3.3.1]non-6-en-9-one (159)</u>

Raney nickel (W-2), (50% slurry in H_2O (pH-10)) was washed with H_2O until neutral, then 95% ethanol (3x 20ml), and then refluxed in analar acetone for 3hrs. Solvent exchanged with absolute ethanol. Approx 1.5g Raney nickel was suspended in absolute ethanol (10ml), (159) (140mg, 0.65mmol) in absolute ethanol (1ml) was added and the resulting solution refluxed for 30min. The solution was filtered and passed through a small plug of Florisil to yield 40mg of a mixture of 3-oxabicyclo[3.3.1]nonane (160) and 3-oxabicyclo[3.3.1]non-6-ene (28).

<u>3-oxabicyclo[3.3.1]nonan-6-yl methane sulphonate (161)</u>

A solution of (156) and (157) (180mg, 1.3mmol), MsCl (0.25mls, 3.2mmol) and dimethylaminopyridine (25mg, 2.0mmol) in dry DCM (10mls) was stirred under N_2 and pyridine (0.53mls, 6.5mmol) was added dropwise. The solution was left stirring for 3 hours, then diluted

with DCM (20mls), washed with cold 0.1M HCl (2x30ml), cold H_2O (2x30ml), dried (Na_2SO_4) and solvent evaporated to yield 300mg of a brown/yellow oil. Columned (medium pressure chromatography) PE/EA, 4:1 to yield 230mg (80%) of a colourless oil.

δ_H ($CDCl_3$) 5.01 (m, 1H, C<u>H</u>OMs (Eq H)), 4.22 (m, 1H, C<u>H</u>OMs (Ax H)), 3.91-3.62 (m, 4H, $C\underline{H}_2$-O-$C\underline{H}_2$), 3.03 (s, 3H, $-SO_2C\underline{H}_3$), 2.6 (m, 1H), 2.2-1.9 (m, 5H), 1.8-1.6 (m, 3H). <u>M/Z</u> (70ev E.I.) 124, 79 (100) <u>M/Z</u> (iBuH C.I.) 219 (M^{-1}), 125 (100).

<u>6-(Trimethyl siloxy)-3-oxabicyclo[3.3.1]non-7-ene (162)</u>[159]

A solution of (158) (540mg, 3.9mmol) in dry DMF (6ml) and triethylamine (1.3ml, 9.4mmol) was treated with chlorotrimethylsilane (0.6ml, 4.7mmol) and the resulting slurry refluxed for 20hr. The cooled mixture was diluted with pentane and washed with cold 5% sodium bicarbonate and H_2O. The pentane was dried and evaporated to yield 550mgs of a yellow oil. Distilled on the Kugelrohr (0.1mm/90°) to give 460mg (56%) of a colourless oil. ν_{max} ($CHCl_3$) 1650cm^{-1} (C=CSt). δ_H($CDCl_3$) 4.8 (t, 1H, =C<u>H</u>, J=3Hz), 3.8-3.4 (m, 4H), 2.5 (m, 1H) 2.1 (m, 2H), 1.8 (m, 3H), 0.15 (s, 9H, $SiMe_3$), <u>M/Z</u> (70ev E.I.) 212 (M^+), 105, 75, 73, 59. <u>M/Z</u> (E.I.) 212.1245 (M, 19%, calculated for $C_{11}H_{20}O_2Si$ 212.1232).

6-(t-butyldimethylsiloxy)-3-oxabicyclo[3.3.1]non-7-ene (163) (Method A)[160]

A solution of (158) (400mg, 2.8mmol) in dry THF (5ml) was added dropwise using a canula to a solution of LDA (1.1eq) at -78° in a dry N_2 atmosphere. The solution was stirred at -78° for 30min and then HMPA (0.8ml) and TBDMSCl (484mg, 3.2mmol) in THF (5ml) were added dropwise. The yellow solution was then left to warm to room temperature (cooling bath removed) and pentane (50ml) was added after 15min. The solution was washed with H_2O, brine and dried ($MgSO_4$), solvent evaporated, azeotroped with CCl_4 (3x30ml) to give 870mg of a yellow oil. Columned on neutral alumina (10.1) to give 410mg (58%) of a colourless oil.

6-(t-butyldimethylsiloxy)-3-oxabicyclo[3.3.1]non-7-ene (163) (Method B)[161]

TBDMS triflate (1.3mls, 7.4mmol) was added to a solution of (158) 0.5g, 3.7mmol) and 2,6-lutidine (0.63mls, 0.056moles) in DCM (5mls) in a N_2 atmosphere. The reaction was monitored by t.l.c. (alumina) and when complete, diluted with DCM (10mls), washed with cold sodium bicarbonate (1x10ml), $CuSO_4$ (aq) (1x10ml). Organic layer dried (Na_2SO_4) and concentrated on rotary evaporator, the residue was taken up in dry ether, separated from any insoluble material and evaporated to yield 1.1g. Columned on neutral alumina using 5% ether in Pet ether (30-40°) containing 1 drop of pyridine as elutant to give 890mgs (95%) of a colourless oil. ν_{max} (thin film)

1660cm^{-1} (C=CSt) δ_H ($CDCl_3$) 5(t, 1H, =C<u>H</u>, J=3Hz), 3.81, (d, 1H, J_{GEM}=10.8Hz) 3.75 (d, 1H, J_{GEM}=10.6Hz), 3.65 (d, 1H, J_{GEM}=11Hz), 3.45 (dd, 1H, J_{GEM}=10.6Hz, J_2=1.84Hz). 2.4 (dd, 1H), 2.10-2.00 (m, H) 1.9 (m, 3H), 0.95 (s, 9H, Si(t<u>Bu</u>)), 0.15 (s, 6H, Si(<u>Me</u>$_2$)) δ_C($CDCl_3$) 155.01 (s, C-6), 108.96 (d, C-7), 79.69 (t, C-4) 72.52 (t, C-2), 41.42 (d, C-5), 34.36 (t, C-8), 34.23 (t, C-9), 34.21 (s, -<u>C</u>(CH_3)$_3$), 32.77 (d, C-1), 30.24 (q, ($C\underline{H}_3$)$_3$), -4.67 (q, Si-($C\underline{H}_3$)$_2$). <u>M/Z</u> (70ev E.I.) 254 (M^+), 197, 105, 75, 73, 59. <u>M/Z</u> (E.I.) 254.1697 (M, 28%, calculated for $C_{14}H_{26}O_2Si$ 254.1700).

<u>3-oxabicyclo[3.3.1]nonan-6-one (158) with 2,2-dimethoxy propane and p-toluene sulphonic acid</u>[162]

(158) (170mg, 1.2mmol) was dissolved in dry DMF (1ml) and 2,2-dimethoxypropane (1ml). PTSA (5mg) in dry methanol (0.05ml) were added and the resulting solution refluxed for 3½hrs. Columned (PE/EA, 8:1) to yield 15mg of a colourless oil, which was the methyl enol ether of 3-oxabicyclo[3.3.1]non-6-one (165). ν_{max} ($CHCl_3$) 1640cm^{-1} (C=CSt). δ_H($CDCl_3$) 4.7 (t, 1H, =CH, J=3Hz), 3.9 (d, 1H, J_{GEM}=11Hz), 3.77 (d, 1H, J_{GEM}=10.7Hz), 3.64 (d, 1H, J_{GEM}=11Hz), 3.5 (dd, 1H, J_{GEM}=10.7Hz), 3.45 (s, 3H, $C\underline{H}_3$), 2.5 (m, 1H), 2.3-2.15 (m, 3H), 2.0 (m, 3H). <u>M/Z</u> (70ev E.I.) 154 (M^+) 124, 95, 71, 55, 41. M/Z (E.I.) 154.0998 (M, 23% , calculated for $C_9H_{14}O_2$ 154.0994). Further elution gave <u>6,6-dimethoxy 3-oxabicyclo[3.3.1]nonane (164)</u> 105mg as a colourless oil. δ_C($CDCl_3$) 4.0 (d, 1H, J_{GEM}=11.4Hz), 3.86 (d, 1H, J_{GEM}=11Hz), 3.69 (d, J_{GEM}=

11Hz), 3.57 (dd, 1H, J_{GEM}=11.4Hz, J_2=2.4Hz) 3.19 (s, 3H, CH_3), 3.15 (s, 3H, CH_3), 2.26 (m, 1H), 1.85 (m, 3H), 1.73 (m, 3H), 1.61 (m, 1H). $\delta_C(CDCl_3)$ 101.57 (s, C-6), 73.27 (t, C-2), 67.86 (t, C-4), 47.26 (q, OCH_3), 47.15 (d, C-5), 47.10 (q, OCH_3), 34.80 (d, C-1), 30.46 (t, C-9) 28.97 (t, C-7), 27.77 (t, C-8). M/Z (70ev E.I.) 185 (M^{-1}), 153, 123, 95, 71, 55, 41.

5-(2-formylmethyl)-3-tetrahydropyranmethyl t-butyldimethyl siloxy carbonyl (167)[160]

(163) (500mg, 20mmol) was dissolved in analar methanol (10ml) and analar DCM (8ml) and was cooled to -78°. Ozone was passed through until starch-iodine paper indicated the presence of excess oxidant as the blue colouration was not sufficient to show that the reaction had gone to completion. On completion the reaction mixture was treated with dimethyl sulphide (0.5ml) and allowed to warm to room temperature. Evaporation and then extraction with PE (30-40°) and H_2O. PE extracts washed with H_2O, dried ($MgSO_4$) and evaporated to yield 540mg of a colourless oil. All attempts at purification proved unsuccessful. Spectral data on crude compound. ν_{max} ($CHCl_3$) 1700cm^{-1} (C=O), $\delta_H(CDCl_3)$ 9.75 (m, 1H, CHO, aldehyde), 4.15 (m, 1H, CH_2O), 3.85 (m, 1H, CH_2O), 3.36 (m, 1H, CH_2O), 2.95 (m, 1H, CH_2O), 2.7 (m, 1H, CH COOTBDMS), 2.35-2.00 (m, 3H, CH_2CHO and $CHCH_2CHO$ (bridgehead), 1.7-1.6 (m, 2H), 0.95 (s, 9H, Si(tBu)), 0.15 (s, 6H, Si(Me_2)). M/Z (iBuH C.I.) 285 (M^+), 255, 227, 211, 171, 155, 143, 127 (100) 113.

Attempted preparation of 5-(2-formylmethyl)-3-tetrahydro pyrancarboxylic acid (166)

(167) (100mg, 0.35mmol) was dissolved in anhydrous THF (5ml) and tetrabutylammoniumfluoride (0.1ml, 1mmol) was added and the solution stirred for 1hr. THF evaporated off and the residue dissolved in ether and washed with brine, dried (Na_2SO_4) and evaporated to yield none of the desired product.

5-(2-formylmethyl)-3-tetrahydropyran carboxylic acid (166) Method A[160]

(162) (450mg, 21mmol) was dissolved in analar methanol (15ml), and analar DCM (12ml) and was cooled to -78°. Ozone was passed through until starch-iodine paper indicated the presence of excess oxidant. On completion the reaction mixture was treated with dimethyl sulphide (0.5ml) and allowed to warm to room temperature. Solvent evaporated to yield 340mg (94%) of a colourless oil. Columned (medium pressure) (PE/EA, 1:1 + 1% formic acid) to give a white solid (290mg, 81%).

5-(2-formylmethyl)-3-tetrahydropyran carboxylic acid (166) Method B[132]

(167) (440mg, 15mmol) was stirred in acetic acid (3ml), H_2O (1ml) and THF (1ml) for 20hr at 25°. The THF was evaporated and the residue dissolved in ether and stirred vigorously for an hour. Washed with brine and then brine back extracted with ether. Organic extracts

dried (Na_2SO_4) and evaporated to yield 280mg of a slightly yellow oil. Columned (medium pressure) (PE/EA, 1:1 + 1% formic acid) to give a white solid (210mg, 81%) m.p. 127-128°. ν_{max} ($CHCl_3$) 3500-3000 (broad) (COOH St), 1700cm^{-1} (C=O). δ_H($CDCl_3$) 9.9 (m, 1H, CHO, aldehyde), 9.0 (br. s, 1H, COOH), 4.19 (m, 1H, C-2, Heq), 3.94 (m, 1H, C-6, Heq), 3.35 (m, 1H, C-2, Hax), 3.05 (m, 1H, C-6, Hax), 2.75 (m, 1H, CH-COOH (bridgehead), 2.35 (m, 1H, CHCH$_2$CHO (bridgehead) 2.31 (m, 2H, CHCH$_2$CHO), 1.4 (q, 2H, CHCH$_2$CH). M/Z (iBuH C.I.) 171 (M^{-1}(100), 153, 129, 111. Found C,55.76, H,7.12. $C_8H_{12}O_4$ requires C,55.81, H,7.02%.

5-(2-formylmethyl)-3-tetrahydropyran methylmethoxy carbonyl (168)[119]

Diazomethane was prepared in the following way. N-methyl-N-nitrosotoluene-p-sulphonamide (4.18g) was dissolved in anhydrous ether (60ml), cooled in ice and a solution of potassium hydroxide (0.8g) in 95% ethanol (20ml) was added dropwise and was left standing for 5min, after which the etheral diazomethane solution was distilled until the ether distilling over was colourless.

(166) (500mg, 29mmol) was dissolved in the minimum amount of absolute methanol, cooled in ice, and an etheral solution of diazomethane was added in small portions until gas evolution had ceased and the solution had acquired a pale yellow colour. This was left until the excess diazomethane had evaporated. The solvent was

then removed to yield 520mg (97%) of a colourless oil. ν_{max} ($CHCl_3$) 1720cm^{-1} (C=O), δ_H($CDCl_3$), 9.9 (m, 1H, CHO, aldehyde), 4.14, (m, 1H, C-2, Heq), 3.92 (m, 1H, C-6, Heq), 3.7 (s, 3H, OCH_3), 3.33 (m, 1H, C-2, Hax), 3.01 (m, 1H, C-6, Hax), 2.7 (m, 1H, CH-$COOCH_3$ (bridgehead), 2.28 (m, 1H), 2.16 (m, 2H), 1.4-1.2 (m, 2H). M/Z (70ev. E.I.) 185 (M^{-1}), 153, 143 (100), 142, 111, 82, 74, 55, 43, 41, 27.

5-(hydroxymethyl)-3-tetrahydropyran ethanol (169)[170]

(166) (100mg, 0.58mmol) was dissolved in anhydrous THF (5ml) under a N_2 atmosphere and cooled to 0°. A solution of diborane in THF (1M) (2ml) was added dropwise and the resulting solution was stirred for 2hr at 0°. H_2O (5ml) was added to hydrolyse the reaction mixture. Extracted with Et_2O (3x25ml), dried ($MgSO_4$) and was evaporated to yield 60mg (66%) of a colourless oil. ν_{max} ($CHCl_3$) 3650, 3450cm^{-1} (-OH), δ_H($CDCl_3$) 3.9-3.1 (m, 8H, CH_2OCH_2, CH_2OH), 2.05-1.1 (m, 10H).

5-(2-formylmethyl)-3-tetrahydropyran carbanal (170)

Pyridinium chlorochromate (410mg, 1.9mmol) was suspended in DCM (3ml) and (169) (100mg, 0.61mmol) in DCM (1ml) was rapidly added at R.T. After 1-2hr the oxidation followed by t.l.c. was complete. The black reaction mixture was diluted with anhydrous ether (20ml), the solvent decanted and the black solid washed twice with

ether. Product was isolated simply by filtration of the organic extracts through Florisil and evaporation of solvent at reduced pressure to yield 54mg (57%) of a colourless oil. ν_{max} ($CHCl_3$) 1710cm^{-1} (C=O), δ_H ($CDCl_3$) 9.85 (m, 1H, CHO, aldehyde), 9.65 (m, 1H, CHO, aldehyde), 4.2 (m, 1H, CH_2O), 3.9 (m, 1H, CH_2O), 3.4 (m, 1H, CH_2O), 3.0 (m, 1H, CH_2O), 2.7 (m, 1H, CHCHO (bridgehead), 2.2 (m, 3H, CH_2CHO and $CHCH_2CHO$ (bridgehead)), 1.8 (m, 2H).

Reaction of 5-(2-formylmethyl)-3-tetrahydropyranmethyl t-butyldimethylsiloxy carbonyl (167) with n-hexyltriphenyl phosphonium bromide

n-Hexyltriphenyl phosphonium bromide (330mg, 0.75mmol) was suspended in anhydrous THF (10ml) under N_2 and cooled to -78°. nBuLi (0.5ml, 0.75mmol, 1.6m) was added dropwise and the resulting orange solution stirred for 30 minutes. After this time HMPA (1.74ml, 0.01mol, 15 equivalents based on phosphonium salt) was added followed immediately by a precooled (-78°) solution of (167) (200mg, 0.7mmol) in anhydrous THF (2ml) via a canula with the transfer completed by washing with THF (2x2ml). The reaction was stirred for 30 minutes at -78° and pentane/Et_3N (10:1, 9ml) was added and the mixture slowly warmed to 20°. Extraction with hexane/ether/Et_3N (70/20/10) (4x30ml) followed by drying of the combined organic phase (Na_2SO_4) and removal of solvent in vacuo yielded 80mg of a yellow oil containing none of the desired product.

Reaction of 5-(2-formylmethyl)-3-tetrahydropyran carbanal (170) with n-hexyltriphenyl phosphonium bromide

n-Hexyltriphenyl phosphonium bromide (110mg, 0.26mmol) was dissolved in anhydrous THF (5ml) under N_2 and cooled to -78°. nBuLi (0.18ml, 1.64M, 0.26mmol) was added dropwise and the resulting orange solution stirred for 30 minutes. At the same time a solution of (170) (40mg, 0.26mmol) was dissolved in anhydrous THF (5ml) and was cooled to -78°. After 30min, HMPA (0.6ml, 3.8mmol, 15 equivalents based on the phosphonium salt) was added, followed immediately by the phosphonium salt via a canula dropwise (inverse addition). The mixture was stirred at -78° for 30min and then warmed to 0° over 1hr. It was then diluted with ether/pentane (10ml, 1:5) and washed with aqueous lithium chloride solution (2x5ml) and brine (1x10ml), dried (Na_2SO_4) and evaporated to yield 60mg of a pale yellow oil, which was found to be a complex mixture.

5-(cis-2-octenyl)-3-tetrahydropyran carboxylic acid (178)

n-Hexyltriphenyl phosphonium bromide (220mg, 0.5mmol) was suspended in anhydrous THF (5ml) under N_2 and cooled to -78°. nBuLi (0.36ml, 0.5mmol, 1.6M) was added dropwise and the resulting orange solution was warmed to -20° and stirred for 30mins. The suspension was recooled to -78° and anhydrous HMPA (1.2ml, 15 equivalents based on phosphonium salt) was added followed by (166) (40mg, 0.23mmol) in anhydrous THF (2ml) via a canula and stirred

for 1hr then allowed to warm to O°. Quenched with ether, evaporated and residue dissolved in ether, acidified with dil HCl (aq) and extracted with ether (3x20ml), dried (Na_2SO_4) and evaporated. Residue dissolved in pentane and solid filtered off. Pentane evaporated to yield a colourless oil. Columned (medium pressure) (PE/EA, 1:1 + 1% formic acid) to yield 41mg (73%) of a colourless oil/solid. ν_{max} ($CHCl_3$) 3500-3150 (-COOH St.), 3020 (=CHSt), 1700cm^{-1} (C=O). δ_H($CDCl_3$) 10.54 (br. s, 1H, COOH), 5.44 (m, 1H, CH=), 5.34 (m, 1H, CH=), 4.15 (m, 1H, CH_2O), 3.93 (m, 1H, CH_2O), 3.35 (t, 1H, J_1=11.2Hz CH_2O), 2.96 (t, 1H, J_1=11.2Hz, CH_2O), 2.66 (m, 1H, CHCOOH), 2,2 (m, 1H), 1.97 (m, 3H), 1.69 (m, 1H), 1.26 (m, 8H), 0.88 (t, 3H, J_1=6.5Hz, CH_3). M/Z 70ev. E.I.) 240 (M^+), 150, 141, 128, 107, 94, 81, 79, 67, 55, 41. M/Z 240.1729 (M, 1.9%, calculated for $C_{14}H_{24}O_3$240.1725).

2-cis-(2-octenyl)-1,3-dioxane (180)[174]

A 0.5M solution of potassium-t-butoxide in anhydrous THF (10ml, 5mmol) was added via a canula to a stirred solution of 2-(1,3-dioxan-2-yl)-ethyltriphenylphosphorane (2.28g, 5mmol) in anhydrous THF (5ml) in a dry N_2 atmosphere to give the orange phosphorane. Stirring was continued at room temperature for 30min and hexanal (10mmol) was added dropwise. The mixture was stirred for 2hr and then poured into H_2O (50ml). Extracted with ether (3x50ml), dried (Na_2SO_4) and evaporated.

Residue columned (PE/EA, 10:1) to yield 870mg (86%) of a colourless oil. δ_H ($CDCl_3$) 5.54 (m, 1H, =C<u>H</u>), 5.44 (m, 1H, =CH), 4.54 (t, 1H, J=5.2Hz, C<u>H</u> ), 4.14 (dd, 2H, J_1=8.12Hz, J_2=4.95Hz, C<u>H</u>$_2$O), 3.76 (td, 2H, C<u>H</u>$_2$O) 2.37 (m, 2H, C<u>H</u>$_2$CH=CH), 2.12 (m, 3H), 1.32 (m, 7H) 0.88 (t, 3H, C<u>H</u>$_3$) δ_C($CDCl_3$) 132.76 (d), 122.86 (d), 102.04 (d, C-1'), 66.98 (t, C-2' and C-4'), 33.47 (t), 31.50 (t), 29.22 (t), 27.41 (t), 25.75 (t), 22.58 (t), 14.08 (q, C-8). <u>M/Z</u> (70ev E.I.) 197(M^{-1}), 122, 87 (100). Found: C,72.49, H,11.39, $C_{12}H_{22}O_2$ requires C,72.68, H,11.18%.

<u>Cis-3-nonenal dimethyl acetal (181)</u>[174]

A solution of (180) (870mg, 4.4mmol) and p-toluene sulphonic acid (3mg, 0.16mmol) in methanol (40ml) was heated at reflux for 2hr, cooled, and neutralised with anhydrous sodium carbonate. After evaporation of the methanol, the product was taken up in DCM, washed with H_2O, dried (Na_2SO_4) and evaporated to yield 620mg. Residue columned (PE/EA, 10:1) to yield 580mg, 71% of a colourless oil. δ_H($CDCl_3$) 5.49 (m, 1H, =C<u>H</u>), 5.38 (m, 1H, =C<u>H</u>), 4.37 (t, 1H, J=5.9Hz, C<u>H</u>$(OMe)_2$), 3.33 (s, 6H, $(O\underline{Me})_2$), 2.37 (t, 2H, J=6Hz), 2.03 (m, 2H), 1.29 (m, 8H), 0.89 (t, 3H, C<u>H</u>$_3$). <u>M/Z</u> (70ev E.I.) 155 ($M-OCH_3$), 122, 114, 87, 75 (100). Found: C,70.96, H,11.84, $C_{11}H_{22}O_2$ requires C,70.92, H,11.90%.

Cis-3-nonenal (182)[174]

A solution of (181) (520mg, 2.8mmol) in acetic acid (12ml) and H_2O (6ml) was stirred at room temperature for 4hr, neutralised with cold saturated sodium hydrogen carbonate, taken up in DCM and dried (K_2CO_3). Solvent evaporated to give 330mg. Residue columned (PE/EA, 10:1) to yield 290mg, 74% of a colourless oil. ν_{max} ($CHCl_3$) 1730cm^{-1} (C=O) δ_H($CDCl_3$) 9.65 (t, 1H, J=2Hz, C<u>H</u>O, aldehyde), 5.68 (m, 1H, =C<u>H</u>), 5.56 (m, 1H, =C<u>H</u>), 3.18 (m, 2H, =CHC<u>H</u>$_2$CHO), 2.03 (m, 2H, C<u>H</u>$_2$CH=CH), 1.29 (m, 6H), 0.88 (t, 3H, C<u>H</u>$_3$). <u>M/Z</u> (iBuH C.I.) 141 (M^{+1}), 112, 87 (100), 75. Found: C,76.87 H,11.61, $C_9H_{16}O$ requires C,77.09 H,11.50%.

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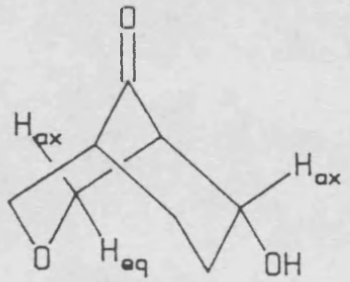
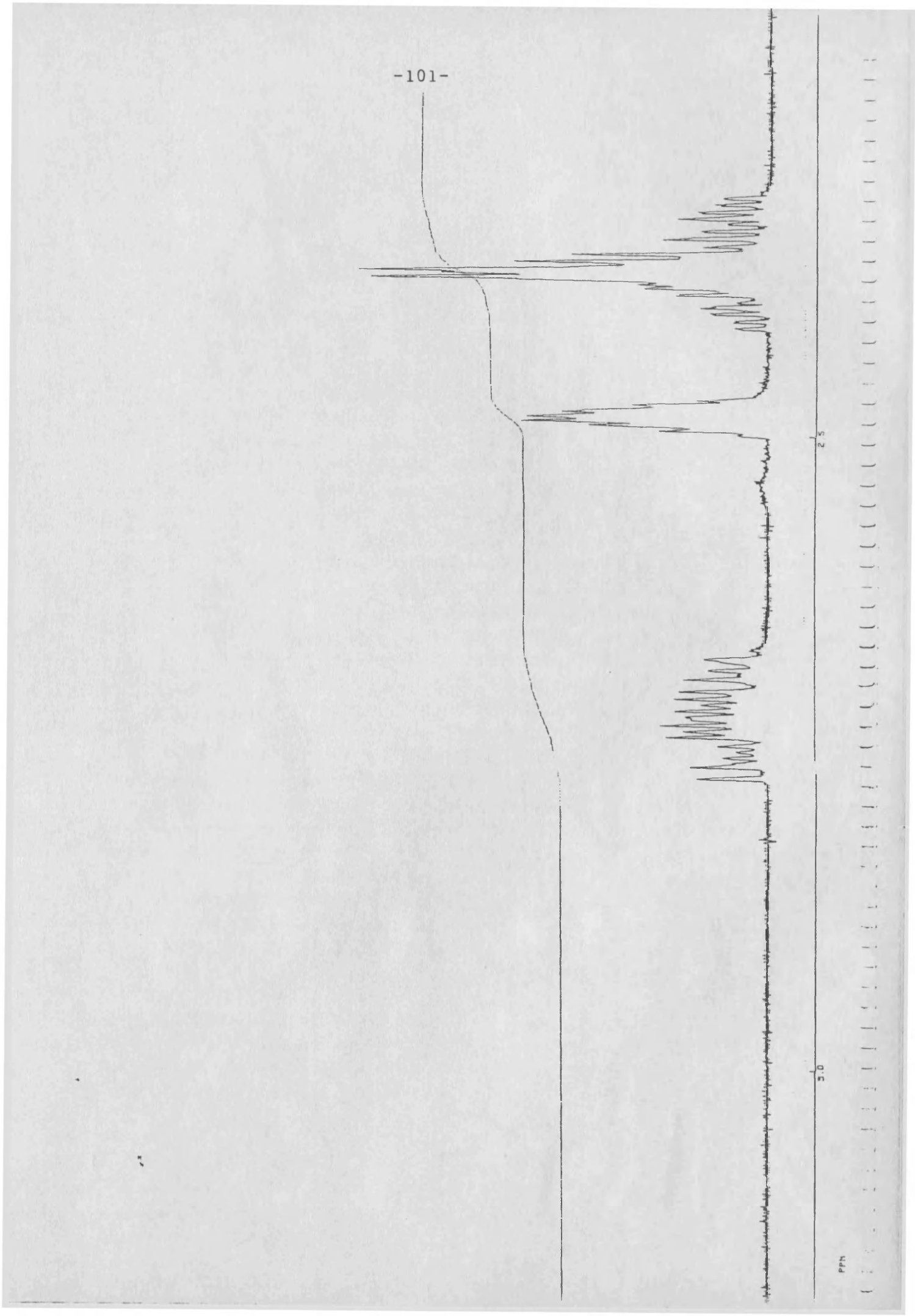
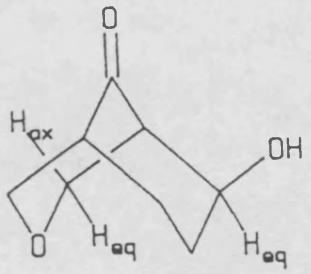


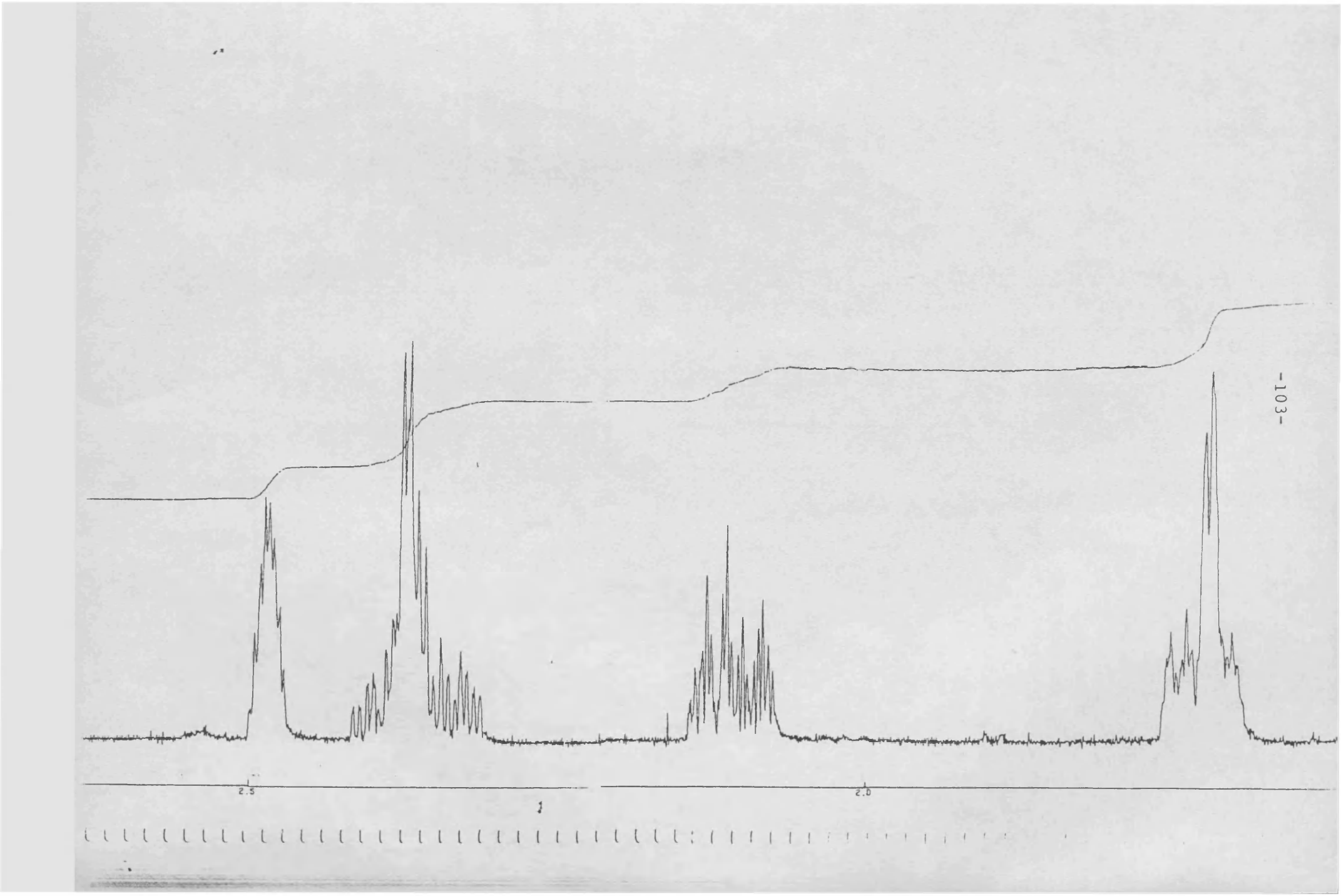
Exo isomer

0.2
5.2


3.0
2.5
PPM



Endo isomer


2.5
2.0
1